Outcome of women 40 years and younger with Ovarian Cancer

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CERTIFICATE

This is a certify that the dissertation entitled “Outcome of women 40 years and younger”, is the original work of Dr. Eileen Lalrinpuii done towards the M.S. Branch II (Obstetrics and Gynaecology) Degree Examination of Tamil Nadu Dr. M.G.R Medical University , Chennai to be held in April 2015.

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INTRODUCTION

Cancer of the ovary is the 9th most common cancer in the world :both sexes put together and the 7th most common cancer among women in the world, (1).Cancer ovary is a lethal female cancer ,because due to its insidious and vague clinical presentation with no established screening method for its detection and two third of cases presenting as advanced disease at presentation it has the highest fatality to case ratio of all female cancers ,it is the most challenging female cancer to treat .(2)cancer ovary is the third most common female cancer in India next to cancer of the breast and cervix ,and the economic burden imposed for its treatment in a resource constraint country like ours will be a huge challenge (3),It is accepted that Epithelial ovarian cancer constitute about 90 % of all ovarian cancers with Germ cell tumors ,sex cord stromal cell tumors, other rarer tumors and metastatic tumors making up the rest . Epithelial ovarian cancer is considered a disease of the old as non epithelial tumors is to thought to be more commoner among the young. Although most of the literature combines clinical features and treatments of epithelial with non-epithelial tumors, these need to be studied separately. It is also not clear how often epithelial tumors affect young women and whether the described bi-modal age distribution clearly separates out epithelial and non-epithelial tumors.(4) It is the aim of this Observational study to look at the clinico-pathologic Pattern in women 40 years and below with ovarian cancer, and compare the survival outcome of Epithelial and non epithelial cancer based on the stage, Histology, Residual tumor and chemotherapy given prior or after surgery effect treatment outcome.

AIMS and OBJECTIVES

1) To look at the clinico-pathologic patterns, in women 40 years and below, with ovarian cancer.

2) To compare the survival outcome of epithelial and non-epithelial cancer in young women.

3) To determine the factors associated with survival and recurrence after treatment for ovarian cancer in young women.

REVIEW OF LITERATURE

Epidemiology: Cancer Ovary is the 7th most common cancer among women ,in fact in the west the sixth most common cause of death among women (5).According to WHO –International agency for Research on cancer 2012 report there were 238719 case of ovarian cancer detected forming age standardized incidence rate of 6.1% with 151905 death forming age standardized mortality rate of 3.8%.As things stands global result shows wide variations in the incidence rate of ovarian cancer ,the lowest rate are seen in china and the highest rates are seen in Russian federation an United Kingdom(6).

In India it is projected that there will be 33,218 ovarian cancer case in 2015, against the projected estimate of 30,482 ovarian cancer case in 2010, as a study done during 2004-2005 showed that it forms about 1.7 to 8.7 percents of all female cancers in various urban and rural population based registries of the National Cancer Registry program(ICMR).(3).over the last 15 years survival of treated ovarian cancer cases in the US (United states) shows modest improvement(6) ,but there is a difference in treatment quality and survival pattern due to economic disparity among different people group (7) The age distribution of epithelial ovarian cancer is that; peak incidence is found in the 56 to 60 age group where as more than 70 % of Germ cell tumors are found in the younger age group in the first and second decade of life .90 % Epithelial Ovarian Cancer are the sporadic form ,and about 10 % of ovarian cancer occur in women are the hereditary type ,susceptibility conferred due to defective genes , The hereditary

ovarian cancer occur roughly 10 years earlier than those of the sporadic type , the much studied and documented hereditary Epithelial ovarian cancer are associated with mutations in the BRCA1 and BRCA2 genes, these mutated genes being found in chromosome 17 and 13 respectively. Though according to western statistics germ cell and sex cord stromal cell tumors form about 5 to 8 % of ovarian cancer , literature review shows that the incidence of Germ cell tumor is higher in the Asian and African population constituting about 15 % of all ovarian cancers and Epithelial ovarian cancer forming about 80 % of all malignant ovarian cancer .A study of the histological distribution of ovarian cancer seen in various studies indicate that that serous type of ovarian cancer is the commonest histological type making up 75to 80 % of epithelial cancer ,mucinous, makes up 10% ,and clear cell, Brenner and undifferentiated type ,each representing less than one percent of epithelial cancers, mucinous epithelial cancer could be the commoner type among the younger age group , it has been hinted that the increase incidence of mucinous type of ovarian cancer could be due to relative increase use of oral contraceptive in the past few decades among women .It is believed that Epithelial ovarian cancers arise from either the surface epithelium of the ovary or from its inclusion cysts within the ovary .Of late there has been an increase in the understanding of the molecular pathogensis of ovarian cancers , there could be two ways for the development of a of serous ovarian cancer resulting in two different types of cancers, one which is low grade slow growing type originating from the coelomic or modified mesothelium, the serous borderline tumor and low grade serous tumour belong to this group ,there is a

growing evidence to suggest that high grade serous cancers arise from the fimbrial end of the fallopian tube.The type 1 low grade serous tumor are genetically stable and are characterized by mutations in KRAS and BRAF . The high grade type 11 serous tumor are rapidly growing , highly aggressive tumor that lack well defined precursor lesions; most are advanced stage at , or soon after ,their inception and are genetically unstable and they harbor p53 mutation(tumor protein p53 , a cellular tumor antigen encoded by TP53 gene, a tumor suppressor gene) .It has often been assumed that that many ovarian cancers are detected late due to its vague presentation, but this could be far from the truth as the cell of origin and the behavior and the type 11 ovarian cancer are indeed different and the starting of the disease and its clinical manifestation could be very short .(8)It is also assumed from findings of previous studies that the stage matched survival rate in the younger age group as compared with those in the older age is better for Epithelial ovarian cancer .(9)

Pathology:

There are four histogenetic categories of ovarian tumours:

1. Surface epithelial stromal tumour (65-70%)
2. Sex cord stromal tumours (15-20%)
3. Germ cell tumours(5-10%)
4. Metastatic tumours

Table: 1 Classification of ovarian tumors

EPITHELIAL OVARIAN TUMOURS	
HISTOLOGIC TYPES	CELLULAR TYPE
1. SEROUS	Endosalpingeal
A. Benign	
B. Borderline	
C. :Malignant	
2. MUCINOUS	Intestinal,Endocervical
A. Benign.	
B. Borderline	
C. Malignant	
3. ENDOMETRIOID	Endometrial
A. Benign	
B. Borderline	
C. Malignant	
4. CLEAR CELL	Mullerian
A. Benign	
B. Borderline	
C. Malignant	
5. BRENNER	Transitional
A. Benign	
B. Borderline proliferating	
C. Malignant	
6. Mixed epithelial type	Mixed
A. Benign	
B. Borderline	
C. Malignant	
7. UNDIFFERENTIATED	May be anaplastic
8. UNCLASSIFIED	
From seroy SF,Sobin LH . *INTERNATIONAL HISTOLOGICAL CLASSIFICTION OF TUMOURS* .9 Histological ovarian tumors.Geneva,Switzerland:World Health Organization,1973,	

Benign serous cystadenoma constitute about half of all of all ovarian serous tumour

Serous tumour of Low malignant potential makes up about 15% of all serous ovarian neoplasm-micropapillary pattern , stromal microinvasion and , extraovarian disease are features of borderline serous tumour , with extra ovarian disease the non invasive implants can be divided into the epithelial and desmoplastic types and the invasive form although uncommon can progress and form metastastatic implants which may progress as a proliferative disease leading to intestinal obstruction and death (10)(11)

Serous carcinoma accounts for 35 to % of all serous ovarian neoplasm , and approximately 75% of ovarian surface epithelial –stromal carcinomas .The high grade (grade 2 to 3) serous carcinomas are the most common surface epithelial carcinomas and are associated with p53 mutations and somatic or germ-line abnormalities of BRCA1 and BRCA2 .

Mucinous tumors accounts for about 15% of surface epithelial neoplasm of the ovary, 80% of all are benign unilocular cystadenomas , they occur in all age group , but more freguently so in the reproductive age group .

Borderline Mucinous tumour account for 15% of all mucinous ovarian tumour of intestinal type, the endocervival type of mucinous borderline tumor are bilateral 40% of the time .

Mucinous Carcinoma, intestinal type account for less than 10% of all mucinous ovarian neoplasms.

Mucinous tumour with pseudomyxoma peritonei- most of these tumours are metastases from primary mucinous tumor of the vermiform appendix

Endometrioid tumour, and low malignant potential endometriod tumours are entities .

Endometrioid carcinoma of the ovary is comparable to grade 1 or 2 endometrioid adenocarcinoma of the uterus.associated with endometriosis 40% of the time and with primary endometrioid cancer of the uterus 20% of the time

Clear cell Carcinomas – occur in the 5^{th} and 7^{th} decade, it could be associated with endometriosis, and may be associated with paraneoplastic hypercalcemia or pelvic venous thromboses.

Transitional cell tumour – they are uncommon, forming about 3% of all epithelial stromal tumors , the benign, borderline and carcinomas can be seen.

Undifferentiated Epithelial tumors lacks histologic features of a specific mullerian cell type.

Mixed Surface epithelial tumors have two or more different histologic cell types.

Sex cord stromal cell tumor demonstrate ovarian, testicular, or a mixture of ovarian and testicular cell differentiation ,manyof this subtype express Inhibin , which could act as a tumor marker. Granulosa cell tumour is the commonest sex cord cell tumor ,it can occur in any age group but more commonly at the mean age of 52.call-exner bodies are characteristic of granulosa cell tumor,juvenile granulosa tumour in 90% of the time occur in females younger than 30 years

Sertoli leydic cell tumour commonly occur in women in their mid -20s . it can occur at a very young age as well as even in the seventh decade of a women's life .one third of sertoli –leydig cell present as virilization .Sex cord tumor with annular tubules , gynandroblastoma and Fibroma-thecoma , and sclerosing stromal cell tumours are other

stromal cell tumors . steroid cell tumours not otherwise specified , leydig cell tumours and stromal luteomas also come under sex cord stromal cell tumors.

Sex Cord—stromal Tumors

1. *Granulosa-stromal cell tumors*

A. Granulosa cell tumor

B. Tumors in thecoma-fibroma group

1. Thecoma

2. Fibroma

3. Unclassified

2. *Androblastomas; Sertoli-Leydig cell tumors*

A. Well-differentiated

1. Sertoli cell tumor

2. Sertoli-Leydig cell tumor

3. Leydig cell tumor; hilus cell tumor

B. Moderately differentiated

C. Poorly differentiated (sarcomatoid)

D. With heterologous elements

3. *Gynandroblastoma*

4. Sex cord tumour with annular tubules

5. Sex cord stromal tumors, unclassified

6. Steroid cell tumours

A.Stromal luteoma

B. cell tumor Leydic

C.Steroid cell tumor, not otherwise classified

Source: Berek & Novak's gynaecology, fifteenth edition

Germ Cell tumors - arise from the primordial germ cells of the ovary ,

Dysgerminomas, immature teratomas, and endodermal sinus tumour are common type of germ cell tumour, Gonadoblastoma , embryonal carcinoma are other type of GCT, mixed germ cell tumors are quite common too.

Histologic Typing of Ovarian Germ Cell Tumors

1. Primitive germ cell tumors

A. Dysgerminoma

B. Yolk sac tumor

C. Embryonal carcinoma

D. Polyembryoma

E. Non-gestational choriocarcinoma

F. Mixed germ cell tumor

2. Biphasic or triphasic teratoma

A. Immature teratoma

B. Mature teratoma

1. Solid

2. Cystic

a. Dermoid cyst

b. Fetiform teratoma (homunculus)

D. Carcinoma

E. Melanocytic

F. Sarcoma

G. Sebaceous tumor

H. Pituitary-type tumor

I. Others

3. Monodermal teratoma and somatic-type associated with dermoid cysts

A. Thyroid tumor

1. Struma ovarii

    a. Benign

    b. Malignant

B. Carcinoid

World Health organization classification of tumours, Pathology and and genetics of of tumour of breastand female organs .Lyon :IARC press,2003

Table No: 2 Germ cell tumor characteristics

Source: atlas geneticsoncology.org

Subtype	Frequency of OGCT	Benign/ Malignant	Uni-or Bilateral	Tumour markers expre	Metastases Route
Dysgerminoma	35-59%	Malignant	10-15% are bilateral	Serum lactic dehydrogenase Serum hCG	Lymphatic System
Endodermal Sinus tumour (EST)	20%	Malignant	Usually Unilateral	AFP (commonly), alpha 1-Antitripsin	Intraperit oneally and hematog enously
Embryonal carcinoma	Rare	Malignant	Usually Unilateral	AFB and hCG	Intraperitoneally
Polyembryoma	Rare			AFB and hCG	
Choriocarc inoma	Very rare	Malignant	Usually Unilateral	hCG	
Teratoma	Immature account for 20% % GCT	Benign or Malignant	12-15% Are bilateral	Immature tera Toma some Times secrete AFP,LDHand And CA 125.	
Mixed GCT	10-15%	Depends on the cell type present		Depends on the cell type present	

Miscellanous ovarian tumors are paraganglioma:myxoma:small cell carcinoma, hypercalcemic type:small cell carcinoma,pulmonary and large neuroendocrine carcinomas .

Secondary tumors of the ovary (Metastases)include, carcinoma,lymphomaor leukemia, melanoma , and sarcoma , the colon and breast are other common sites to metastasize to the ovary.

Fallopian tube carcinomas and peritoneal cancers are treated the same as ovarian cancer and evidence suggests that these disease have common pathogenesis and maybe initiated in the fallopian tube(8)

Results of studies of incidence, histologic, patterns, prognosis and outcome of Epithelial ovarian tumor in the last 3 to 4 decades. A study done in France 1979:showed that fertility sparing surgery was feasible for young reproductive women **(12)**

Outcome of epithelial ovarian cancer in women under 40 years of age treated with platinum-based chemotherapy.1999**(13)**

Results:These results suggest that there are biological differences in the behaviour of serous carcinoma of the ovary in women of reproductive age compared with older women

Clinical features of epithelial ovarian cancer in young reproductive women a study done in Japan 1995 showed that the incidence of mucinous cystadenoma in women below 40 years was higher than that found in above 40 years

Clinical characteristics and prognosis of epithelial ovarian cancer in young women a study done in china over a period of 13 years(1980-2003) the result of their study showed that serous adenocarcinoma was the commonest cancer (56%) followed by mucinous adenocarcinoma (30.9%)followed by well differentiated tumor(25.4%) and moderately differentiated (15.5%) and poorly differentiated tumor , mostly with unilateral involvement of the ovary, carrying a good prognosis with fertility preserving surgery found to be safe for stage 1a and grade 1 disease , and they found out that pathological grade and residual tumor size were independent prognostic factor

Demographic clinical and prognostic characteristics of primary ovarian, peritoneal and tubal adenocarcinomas of serous histology — A prospective comparative study(14)

Result: Primary serous peritoneal cancer has the shortest overall survival among the three,

This study was the largest prospective study comparing primary peritoneal, ovarian and fallopian tube carcinomas of serous histology

There is an increased risk of developing serous primary peritoneal cancer depending on the parity and obesity of the individual .

Outcomes of malignant ovarian germ-cell tumors treated in Chiang Mai University Hospital over a nine year period.(15) This was a clinico- pathological study with survival pattern .of the 72 cases recruited,the mean age was 21.6 years and 11.8% were pre-menarchal . The two most common symptoms were pelvic mass and pelvic pain. Two-

thirds of the studied patients presented at an early stage. The common histology in descending order of frequency were: 1. immature teratoma (34.2%) 2. endodermal sinus tumor (28.9%),3. dysgerminoma (25%),4. mixed type (10.5%) and 5.choriocarcinoma (1.3%). Treatment with fertility sparing operations and adjuvant chemotherapy with a BEP regimen showed a good outcome. An advanced stage was found to be prognostic factor for recurrence.

Histologic pattern, bilaterality and clinical evaluation of 957 ovarian neoplasms: A 10-year study in a tertiary hospital of eastern India(16)

The aim of this study was to find morphologic pattern of ovarian in different age group along with bilaterality. They found out that benign disease was common in the 20-40 age group, with earlier presentation of malignant tumour at at 40-50 age group. The histological types seen idecreasing order was 1.serous cystadenoma (29.9%),2. mature teratoma (15.9%) 3. mucinous cystadenoma (11.1%).60.9% of the malignant tumour were the epithelial type serous cystadenocarcinoma forming 11.3% of all the epithelial malignant tumor.

Regarding bilaterality Metastatic tumors were found to involve the bilateral ovaries in 72%, while 49.5% of malignant serous tumors were bilateral. Borderline serous tumors showed bilateral involvement more commonly (27.4%) than borderline mucinous tumors (15.7%). Most of the malignant tumors presented as stage III (60%) or stage II (20%) disease. The overall survival rate was 85% for stage I tumors, 65% for stage II, 30% for stage III and 15.5% for stage IV tumors.

To summarize the various studies it appears that for low stage disease conservative surgery yields good result and as far as the common histology in the young women results are concern results are conflicting as in some studies mucinous tumor seems to be more and other studies showing serous histology as the common pathology. The prognosis for stage and histology matched disease could be better in the young and there could be a difference in the biological behaviour of serous carcinoma in younger women. A study of the clinicol-patological pattern and outcome of primary peritoneal, ovarian and fallopian tube serious carcinoma showed worse prognosis for primary peritoneal cancer. A number of studies of the borderline tumor underscore the importance of proper pathological staging of each tumor and the importance of sub-classification of the extra-ovarian disease to invasive or non invasive type as the invasive type has the propensity for progress forming peritoneal implants and progressing to widespread intra-peritoneal disease which may lead on to bowel obstruction and death.

Clinical features: More than 80% of of ovarian cancer are seen in postmenopausal women, 56 to 60 years is the peak age for invasive EOC. About 30% of ovarian tumour in postmenopausal women are malignant, whereas only about 7% of malignant ovarian tumor are malignant in premenopausal women.

The average age for borderline tumor to occur is 46 years .

Etiology : Broadly speaking ovarian cancer genesis is associated with low parity and infertility. Endometriosis,polycystic ovarian syndrome, use of an intrauterine devise ,and cigarette smoking(for mucinous carcinomas) are also known risk factors too (17) (18),)factors that are associated with decrease risk include :previous pregnancy ,history of breast feeding ,oral contraceptives use, an tubal ligation . Although a variety of epidemiologic variables like increased talc use and milk consumption are linked with ovarian cancer, and decreased risk associated with tubal ligation ,but none is as strongly correlated as prior reproductive history . As far as prevention is concern oral contraceptive pills usage is the only chemo-preventive measure identified (17)

Prevention: Ovarian cancer is seen frequently among women with infertility or low parity. Having one child reduces the risk of ovarian cancer by 30 to 40 %. Oral contraceptive pills usage for 5 years or above confers a relative risk reduction of 50 %.
Bilateral salpingo-oophorectomy significantly reduce the risk of ovarian cancer in the high risk individuals, but does not totally eliminate it, as the entire peritoneum lining is still at risk.

Screening: Randomised control trial of ovarian cancer screening using a strategy that included sequential CA 125 and transvaginal ultrasound has been found to increase median survival. Annual transvaginal ultrasound screening has been found to decrease disease stage at detection and increase case specific ovarian cancer survival in a recent trial involving 25,327 women. In spite of this, there is no established screening method in place for ovarian cancer.

The multimodal approach for screening using imaging and a tumor marker is promising. Tumor markers are molecules or substances produced by or in response to neoplastic proliferation,that enter the circulation in detectable amounts. They indicate the likely presence of cancer and provide information about its behavior. For screening protocols, the value of the marker depends on its sensitivity (proportion of cancer detected by a positive test) and specificity (proportion of those without cancer identified by negative test). The most limiting factor is a lack of specificity for most tumor markers and a low positive predictive value. However, tumor markers have an important role to play for differential diagnosis, screening, determining therapeutic efficiency, detecting recurrences and predicting prognosis.

A variety of imaging modalities are in use to identify the morphological characteristics of cancer. These features may not be highly specific but may serve as a sensitive marker. Detailed tumor morphology can be quantified for use in a variety of scoring systems.

The ultrasound features which are used for scoring are: 1. Multilocularity, 2 .Bilaterality 3. Solid areas 4. Ascites and 5. Intra-abdominal metastasis.

Different screening strategies may incorporate 1. CA 125 and Ultrasonography,

2. Ultrasonography and OVA1, 3. Risk of Malignancy Index (RMI).

RMI I gives a score of 0 for no feature and a score of 1 for I feature,, and score of 3 if more than I feature appreciated. This scoring system, conceptualized by Jacobs et al in 1990, takes into account the ultrasound score (U), the menopausal state (M) and, the absolute CA125 value in U/L. RMI = U x M x CA125 and a score > or = to 200 gives a sensitivity of 85% and specificity of 97% for predicting malignancy

Table 3. Risk of malignancy Index (RMI)

VARIABLES	FINDINGS	PROCEDURE
Menopausal status , has the women had no period for a year or more?	Premenopausal	Assign 1 point
Is she 50 or older with a previous hysterectomy	Postmenopause	Assign 4 points
1.Ultrasound finding are there cyst with more than 1 chamber, **2.are there cyst with solid areas inside them** **3.Is there evidence of metastases** **4.Ascites** **5.are there lesions on both ovaries**	**0-1 findings suggestive of malignancy**	Assign 1 point
	2-5 findings suggestive of malignancy	ASSIGN 4 POINT
Serum Ca-125	Level in U/Ml	FORMULA 1

Source: SU10_ALGO_TABLE_DIOGNOSIS –gif

http://protomeg.ticsnetwork.c

The morphological features or tumor structure is also taken account in this system.

Score of more than or equal to 5 is significant and use as a cutoff

Doppler pulsatility index of <1 and Resistance index of <0.4 points to malignancy. There is no diagnostic benefit of doppler over sonograpic tumour malignancy index alone.(19)(20)

Some of the new biomarkers which could aid in screening are the use of proteomic patterns(which are proteins and protein fragments that circulate in the blood indicating early changes caused by genetic mutation) to identify cancer using enhance laser desorption time of flight (SELDI-TOF) technology.

There is a suggestion in the literature that total and ionized calcium could help in detection of ovarian cancer. Leukocytosis detected preoperatively along with thrombocytosis could be of prognostic significance as they are found to be elevated in advance cancer (21)

Biomarkers: Although a vast number of serum markers have been investigated few have been validated for clinical use :

1. CA 125 (cancer antigen 125) sensitivity is 50% for early stage disease, sensitivity is more in postmenopausal women .

2. OVA 1 -5 proteins , CA 124 -11, Beta -2 microglobin, Transferrin, Transthyretin,

Alfa fetoprotein A1.

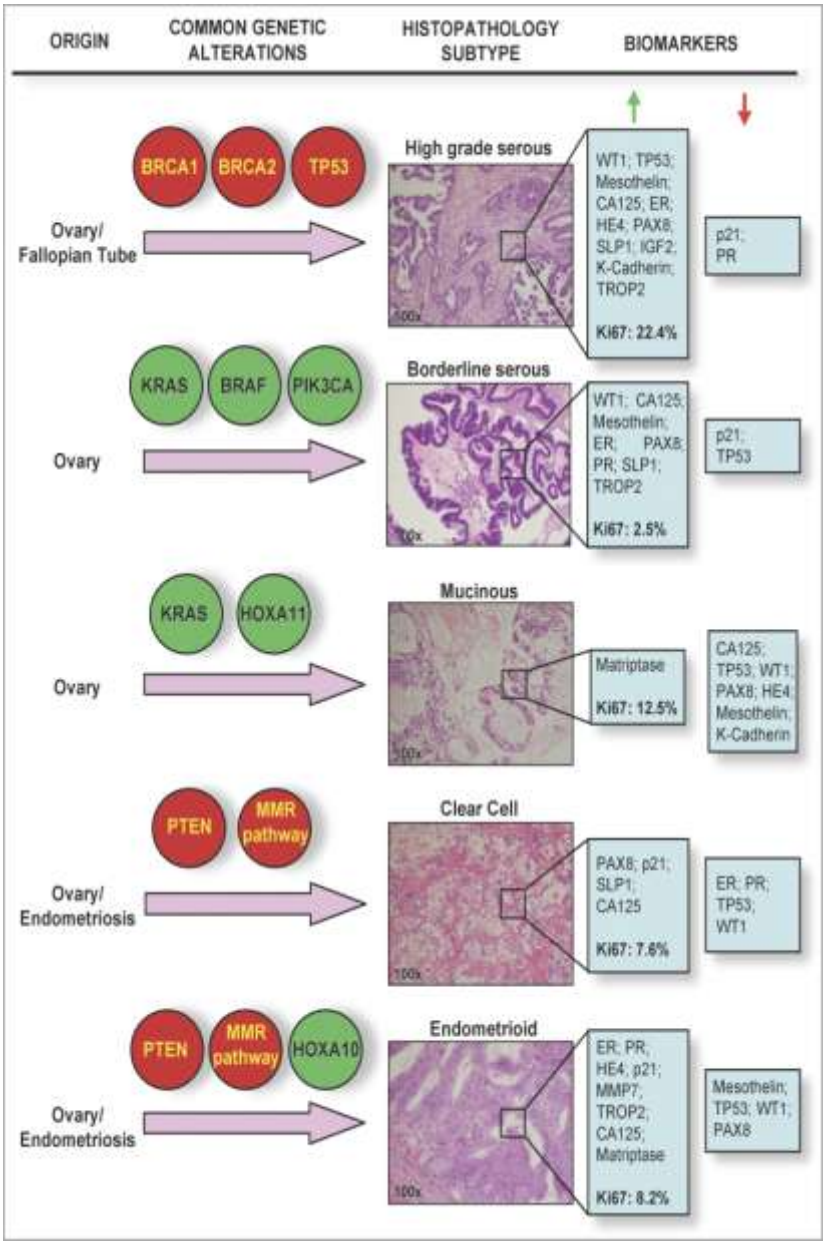
Premenopuasal cut-off: There is a low probability of malignancy if OVA 1 < 5, high if >5

Postmenopausal cut-off: There is low probability if OVA1 <4.4, high if >/=4.4.

Sensitivity is 99% for epithelial ovarian cancer.

3.HE4 Human epididymis protein 4 produced by WFC2 gene expression – HE4 is expressed more in serous and endometrioid cancer , ROMA includes CA125 and HE4.The other biomarkers are OVX1, Prostaisin, Osteopontin, cytokeratin Kallikrein, AFP, Inhibin,

Activin , CA 19.9 for detecting CA 125 negative mucinous ovarian tumor , and VEGF , vascular endothelial growth factor a promoter of angiogenesis ,important in tumor growth and metastasis .



Source: openi.nlm.nih.gov

Figure: 1 Origin of Biomarkers

Genetic Risk for Ovarian Cancer: **T**he highest risk of ovarian cancer is associated with family history of cancer ,the BRCAI(chromosome 17) and BRCA2(chromosome 13) cancers occur in women approximately 10 years younger than those with sporadic types therefore it has been suggested that screening may be initiated at the age of 35 years or 5 to 10 years earlier than the sign of first diagnosis of ovarian cancer in the family (22)(23)(24)(25). Lynch syndrome or hereditary nonpolyposis colon cancer include multiple adenocarcinomas , involves colon, endometrial and ovarian cancer and other malignancies of the gastrointestinal and genitourinary systems (26) , mutations that are associated with this syndrome are MSH2/MLH1, PMS, PMS2 .Some of the management protocol in place for women at high risk for ovarian cancer of genetic origins are genetic counselling and testing for BRCAI and BRCA2 and 6 monthly ultrosonography, and OC Pills usage and prophylactic bilateral salpingo-opherectomy and even Hysterectomy(27)(28)(29)The. **Founder effect** certain ethnic group like the Ashkenazi Jews, Icelandic women have higher carrier rate of BRCA1 and BRCA2 mutated genes.

The high risk individuals are now recommended to have ultrasound screening 3 monthly from the annual screening they use to follow.

Symptoms: Most women have vague and non specific symptoms, in premenopausal women with early stage disease, irregular menses , bowel and urinary(urgency and frequency) symptoms could be the presenting symptoms.. In advance–stage disease, patients have symptoms related to the presence of ascites, omental metastases , or bowel metastases like abdominal distension, nausea and anorexia and early satiety . In one survey of 1,725 patients with ovarian cancer 95% recalled symptoms before diagnosis, including 89% with stage 1 and 2 disease and 95% with stage 3 and 4 disease , some 70% had GI

symptoms. Meta analysis of 21 mostly retrospective studies shows that most women had pelvic and abdominal symptoms with epithelial ovarian cancer(30)(31). The pattern and quality of symptoms appear to differ among patients with cancer in terms of frequency / regularity or intensity of the symptoms, one study showed the symptom recurring 20-30 times versus the 2-3 times per month seen with the primary care patient((31).With the great need to detect ovarian cancer early so as to improve survival a symptom index(SI) has been developed to aid clinicians in evaluating women for early symptoms of epithelial ovarian cancer. Further validation studies are needed for this index and it is not yet recommended for routine clinical use.

Signs : The most important sign is the presence of a pelvic mass on examination. A solid irregular fixed mass is highly suggestive of ovarian malignancy .If and upper abdominal mass or ascites is present it is almost certain it could be a malignancy.

Diagnosis: Ovarian cancer survival rate will improve through early detection of the disease, but effective screening method has not been established and to this end research is continuing to find out the diagnostic method with high sensitivity , specificity and positive predictive value, as benign neoplasm , functional cysts of the ovary should be discriminated from a malignant tumor..

With research and the results of use of HE4 a tumor marker, repeat study of HE4 as a tumor marker shows that ROMA ,RMI and CA 125 have their place but HE4 is a stronger predictive marker of malignancy and that the use of computed tomography for diagnosis of intraperitoneal spread of the disease will add to the specificity of HE4 as a tumor marker. (32) **.**Serum CA 125 measurement is and established protocol in all gynecology-oncology centers, the use of RMI (risk of malignancy index) which combines CA125 value

,ultrasound features and menopausal state to predict risk of malignancy is established. The sensitivity of CA125 that in 80-85 % of women with advance stage of epithelial cancer it is found to be high , and only 50% of the time in early disease it is elevated and it is found to be elevated in many benign conditions as uterine myomas,cystadenoma of ovary,and pelvic inflammatory diseases the specificity of the test is reduced to 75%,(33).Coming back to RMI the ultrasound score in RMI scoring is calculated as follows one point is given for the presence of ; multilocularity ,ascites and the presences of metastasis in the abdomen ,a score of 0 which indicate absences of any ultrasound features or a score of 0 to 1 or, a score 2 or more will give a U value of 1 or 3 , and the menopausal status represented by the letter M is allocated a score of 1 for premenopausal state and 3 for post menopause, the menopause score, CA 125 values at the time of evaluation and the ultrasound score were used to complete RMI work analysis. Studies have shown of late that HE4 can emerge as a promising tumor marker for the diagnosis of ovarian cancer ,not many study have been done to test if ROMA or RMI has a better diognostic performance, a multicenter study shows that ROMA could be a better system with a a better predictive value as compared to RMI for diagnosis of malignant ovarian cancer (34).

Differential diagnosis: Pelvic inflammatory disease, endometriosis,pedunculated uterine myomas .

Patterns of spread:

1. Transcoelomic
2. Lymphaticc
3. Hematogenous

Prognostic factors : Can be grouped into Pathologic, Biologic and Clinical factors .

Important prognostic variables among the Pathologic factors are the morphology, histologic pattern and architecture and grade of the disease, grade of the lesion is not taken as an independent prognostic factor .Clear cell carcinomas have the worse prognosis (35)(36).Clinical factors in addition to stage , the residual disease after primary cytoreduction, the volume of ascites , patients age and performance status are all independent prognostic variables(37) , intraoperative rupture or spillage does not worsen prognosis. For early stage disease poor prognostic variable are tumour grade (38), capsular penetration, surface excrescences and malignant ascites and not iotrogenic rupture (39) Epithelial carcinoma of the ovaries, fallopian tubes, and peritoneum are clinically similar.

Preoperative evaluation: Preoperative testing include: imaging and other testing for metastases, tumor markers for diagnosis and as a baseline for post treatment surveillance,and testing for hereditary cancer syndrome.

Initial surgery for Ovarian Cancer: Ovarian epithelial malignancies are staged according to FIGO system, it is based on surgical findings at surgical exploration, it is important to have a thorough staging because subsequent treatment depends on it.FIGO staging of ovarian cancer 1988 was used for this study ,the latest FIGO staging 2014 is as follows:

2014 FIGO ovarian, fallopian tube, and peritoneal cancer staging system and corresponding TNM.

I Tumor confined to ovaries or fallopian tube(s) T1

IA Tumor limited to one ovary (capsule intact) or fallopian tube, No tumor on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings

T1a

IB Tumor limited to both ovaries (capsules intact) or fallopian tubes

No tumor on ovarian or fallopian tube surface

No malignant cells in the ascites or peritoneal washings

T1b

IC Tumor limited to one or both ovaries or fallopian tubes, with any of the following:

IC1 Surgical spill intraoperatively

IC2 Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface

IC3 Malignant cells present in the ascites or peritoneal washings

T1c

II Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp) T2

IIA Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries T2a

IIB Extension to other pelvic intraperitoneal tissues T2b

III Tumor involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the

peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes T3

IIIA Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis T1,T2,T3aN1

IIIA1 Positive retroperitoneal lymph nodes only (cytologically or histologically proven)

IIIA1(i) Metastasis ≤ 10 mm in greatest dimension (note this is tumor dimension and not lymph node dimension) T3a/T3aN1

IIIA1(ii) Metastasis N 10 mm in greatest dimension

IIIA 2 Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes T3a/T3aN1

IIIB Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes T3b/T3bN1

III C Macroscopic peritoneal metastases beyond the pelvic brim N 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1) T3c/T3cN1

IV Distant metastasis excluding peritoneal metastases

Stage IV A: Pleural effusion with positive cytology

Stage IV B: Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2)

Any T, Any N,

M1

(Note 1: includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

(Note 2: Parenchymal metastases are Stage IV B)

T3c/T3cN1)

Notes: 1. Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ.

2. Parenchymal metastases are Stage IV B.

Technigue for surgical staging

A**.** Staging procedure includes Mid-line incision on the abdomen.

B.Collection of ascitic fluid / peritoneal washing (50-100 ml saline instilled and recovered)

C.Systematic exploration of all the intra-abdomianl surfaces and viscera.

D.Biopsy of all the suspicious areas or adhesions of the peritoneal surfaces,

E.Sampling of the diaphragm by biopsy or scraping ,

F.Omentectomy and

G. Retroperitoneal space exploration .

Results- Metastases in apparent stage 1 and 11 epithelial ovarian cancer can occur in as many as 3 in 10 patients.

Early stage ovarian cancer – The primary treatment for early stage 1 Epithelial ovarian cancer is surgical –that is total abdominal hysterectomy ,bilateral salpingo-oopherectomy , and surgical staging.

Borderline tumors –the principal treatment is the surgical resection of the primary tumor.

Fertility Preservation in Early stage ovarian cancer can be advised for stage 1A-1C with grade 1 to 2 disease , followed by post treatment surveillance with CA125 level determination and routine transvaginal ultrasonography , then ovary and uterus may be removed at the completion of child bearing.

Advanced Stage Ovarian cancer- if the performance status of the patient is good patient should undergo an initial exploratory procedure with removal of as much disease as

possible along with the metastatic disease this procedure is referred to as debulking or cytoreductive surger (40) (41)(42). The pre-operative assessment of respectability is limited ,CA 125 cut –off of 500 U/mL level has been suggested as a means of predicting the probability of optimal resection . The rationale of cytoreductive surgery is 1. The physiologic benefit of tumor excision and 2. The improved tumor perfusion and increased growth fraction.both of which increase the likelihood of response to chemotherapy or radiation therapy. Large tumor mass has higher chance of having phenotypically resistant clones of cells.

Cytoreductive surgery include –Incision of the abdomen by vertical midline incision , ascitic fluid / peritoneal washing collection , exploration and biopsies in a systematic manner assessing the status of the pelvic pelvic organ ,small and large intestine ,mesentery, appendix, stomach, liver gall bladder, spleen , omentum ,both diaphragms dome, entire peritoneum, retroperitoneal structure such as kidneys,pancreas, and lymph nodes palpation along with palpation of the umbilicus is also for any resectable tumor .

Retoperitoneum is accessed by dividing the round ligament as laterally as possible and then developing the pararectal and paravesical spaces,the pararectal space is developed by sharp dissection between the medial leaflet of the broad ligament and the external and internal iliac vessels taking care to protect the ureter on the medial leaflet and avoiding dissection lateral to internal iliac artery which lie inferior and medial to the external iliac vessels ,the paravesical space is created by sharp dissection toward the pelvic floor between the superior vesical artery and and the external iliac vessels , the pelvis mass be entered from the prevesical space or either paracolic gutter ,A retroperitoneal approach is best if the pelvis appears frozen, this approach allows resection of tumor encroaching on the bladder

or bowel from lateral aspect beneath the bladder and posterior cul de sac reflection, biopsy is taken from all suspicious sites.Pseudomyxoma peritonei can be associated with benign, malignant and borderline tumor , Frozen section maybe sent,omentectomy and salpingo-oopherectomy , lymph node sampling and appendectomy may follow.

Factors which may limit achievement of optimal cytoreduction maybe technical or related to poor performance status. Factors that preclude optimal cytoreduction include

1.Presence of extraperitoneal or retroperitoneal disease or large tumor bulk

2. Extensive bowel involvement

3. Parenchymal liver and lung involvement

4. Presence of massive ascites

5. Ability of patient to tolerate cytoreduction, based on age, performance status, medical co-morbidities and preoperative nutritional state.

Cytoreduction is associated with increased survival. Splenectomy maybe done if tumor nodules extend into the splenic hilum; partial hepatic resection too is an option if a lobe is involved, in case of diaphragmatic disease stripping or resection can be done; bowel resection could be an important part of cytoreduction; there may be a need to do bladder and ureteral resection, placement of a port for intraperitoneal chemotherapy may be done simultaneously.

Optimal cytoreduction maybe considered if there is no residual tumor at the end of the surgery (R0) although many would consider residual nodules < 1 cm as adequate.

Interval cytoreduction. following chemotherapy is an option if primary cytoreduction is deemed improbable or if patient is not fit for extensive cytoreductive surgery.

Laparoscopy. In early stages, it may be done if patients are selected carefully, but many surgeons think it is not prudent to do laparoscopic surgery in ovarian cancer .

Adjuvant treatment:

Early stage (IA) low risk ovarian cancers do not need further adjuvant treatment.

Early stage (IA and IB) high-risk ovarian cancers are treated with three cycles of adjuvant carboplatin and paclitaxel chemotherapy.

The current GOG trial includes patients with high risk stage I and II disease and offers three cycles of carboplatin and paclitaxel followed by randomizing them either to observation versus 26 weeks of weekly low dose paclitaxel (40mg/m2). High risk stage I is defined as stage IA or IB grade 3, stage IC or clear cell carcinomas.

Radiation therapy for low stage epithelial ovarian cancer is by intraperitoneal radiocolloids or whole abdominal radiotherapy.

Table: 4 Chemotherapy drug protocol for Advanced stage ovarian cancer

Combination chemotherapy for advanced ovarian cancer :Recommended Regimen				
Drugs	Dose	Administration (hr)	interval	No.of treatment
Standard Regimen				
Paclitaxel Carboplatin	175 mg/m2 AUC =5-6	3	Every 3 weeks	6-8 cycles
Paclitaxel	135 mg/m2	3	Every 3 weeks	6-8 cycles
Alternative drugs[a] (can be given with platinum)				
Topotecan	1.0-1.25 mg/m2 4.0 mg/m2		Daily x 3-5 days Every 3 weeks or weekly	
Gemcitabine	800-1,000 mg/m2		Every 3 weeks	
Doxorubicin, liposomal	40-50 mg/m2		Every 4 weeks	
AUC , area under curve dose by Calvert formula; Drugs that can be substituted for paclitaxel if hypersensitivity to that drug occurs.				
Patients who cannot tolerate IV chemotherapy can be given an oral alkylating agent or oral etoposide.				

Consolidation and maintenance of clinical response to first line chemotherapy- the benefit of consolidation and maintenance chemotherapy is doubtful, patient and physicians may consider prolonged single agent paclitaxel an option, but it should not be considered as standard care.

Administration of chemotherapy and amelioration of toxicity Dose and schedule can be adjusted to reduce toxic reaction.

Radiation therapy is an alternative to first line combination therapy for selected patients with metastatic disease.

Hormonal therapy as a first line drug is not practiced but may be used to suppress recurrent disease

Immunotherapy is on trial.

Treatment Assesment may be done using tumor markers ,rising level during treatment indicate treatment failure,radiologic assessment with Computed tomography or PET scan or fluorodeoxyglucose FDG-PET can be done .

Second look laparotomy is not recommended, but **second look laparoscopy** could have a role.

Secondary treatment . Secondary cytoreduction or second line chemotherapy can be administered.

Table 5: **Second line chemotherapy in recurrent or persistent Epithelial ovarian cancer**

Drugs used in Platinum and Taxane sensitive Disease
Response Rate 20-40%
Cisplatin
Carboplatin
Paclitaxel (Taxol)
Docetaxel (Taxotere)
Drugs used in Platinum and Taxane resistant and Refractory disease
Response Rate 10-25%
Topotecan (Hycamtin)
Etoposide (oral) (VP-16)
Liposomal doxorubicin (Doxil)
Gemsitabine (Gemsar)
Hexamethylmelamine (Altretamine)

Platinum sensitive disease Platinum and paclitaxel regimen in patient who have not received paclitaxel in their primary chemothereupeutic regimen may provide slight advantage .

Platinum resistant and refractory disease – single agent chemotherapeutic drugs like paclitaxel, docetaxel, topotecan , liposomal doxorubicin, gemsitibine , oral etoposide, tamoxifen and bevacizamud can be tried

Hormonal therapy as second line therapy – 15 to20% response rate with tamoxifen is seen in well differentiated carcinomas of the ovary, Aromatse inhibitors e.g letrozole, anatrozole, and exemestane are also being used.

Targetted therapies Incorporation of angiogenesis inhibitors (bevacizumab) and other VEGF inhibitors for first line treatment is not recommended as of now, but may be used as a maintenance therapy.

Dose intense second line chemotherapy, or

High dose chemotherapy and Autologous bone marrow transplantation may not show significant difference in progression free survival (PFS) or overall survival.

Whole abdominal radiation may be effective in a small subset of patients, but is associated with relatively high morbidity.

Intestinal obstruction maybe related to mechanical obstruction or to carcinomatous ileus – parental alimentation may be the best option for this group.

Genome wide tumor analysis if the molecular tumor profile of each individual patient can be maintained ,this will help in selecting molecular targeted treatment just right for the patient. (43)

Survival : There is a trend toward improved survival for ovarian cancer(44). Survival rate for all stages from 1976 to 1978 was 29.8%,, for the interval of 1999 to 2001 the survival rate was 49.7%

The 5 year relative survival rate of ovarian cancer is poor at 40-45%(45). The five year survival rate for carefully and properly staged patient with stage 1 disease is as high as 94%, for stage 11 is 73%, for stage 111 or 1V 28% (46)

The survival of patients with borderline tumor is excellent , with stage 1 lesion having a 98% 15 year survival (47) . Patients who relapsed within 6 months of completing first line chemotherapy are classified as platinum resistant and have a median survival of 6-9 months and a 10% likelihood of responding to chemotherapy, patients who progress while on treatment are classified as platinum refractory disease.

Non epithelial tumours account for about 10% of all ovarian cancers,in the first two decades of life , almost 70% of ovarian tumour are of germ cell origin and 1/3 of these are malignant , in contrast to the relatively slow growing EO tumour the Germ cell malignancies grow rapidly, The most common type of GCT are dysgerminomas, immature teratomas and Endodermal sinus tumour , although 20-25% of all benign and malignant ovarian neoplasm are are of germ cell origin only about 3% are malignant,it account for 5 % of all ovarian cancer according to western figure where as the observation in Asia and Africa shows that 15 % of ovarian cancer are of Germ cell type and epithelial ovarian cancer is relatively less. The survival rate for all stages, ages and types are as follows: **Table 6. Survival of ovarian cancer.**

Epithelial ovarian cancer Stage	**5 year survival**
Stage I	94 %
Stage II	73 %
Stage III	28 %
Stage IV	10 %

Non Epithelial Ovarian cancer Histologic type	**Stage**	**5 years survival**	**10 years survival**
Germ cell tumour (Dysgerminoma)	I A Advanced	95% 68-83%	
Immature Teratoma	I All stages	90-95% 70-80 %	
Yolk sac tumour	All stages	60-70 %	
Granulosa cell tumour		>95 %	90%
Sertoli Leydig tumour		70-90%	

Germ cell tumour survival range for all stages of Germ cell tumours ranges from 60-100%**(48)(49)** The most effective chemotherapy uses bleomycin, etoposide and cisplatin (BEP)**(50)(51)**. Stromal cell tumours include granulosa cell tumours, which are low grade malignancies in premenopausal women. They can be treated conservatively and adjunct chemotherapy is of unproven value. Fertility sparing surgery for young women with malignant germ cell tumor may be done **(52)**. Metastatic tumours to the ovaries are most frequently from the breast and gastrointestinal tract**(53)**. There are limited studies conducted in India to study the clinicopathologic pattern and survival pattern among younger women with this malady. The overall survival of all age of epithelial ovarian tumor is 40 %**(54)**

METHODS

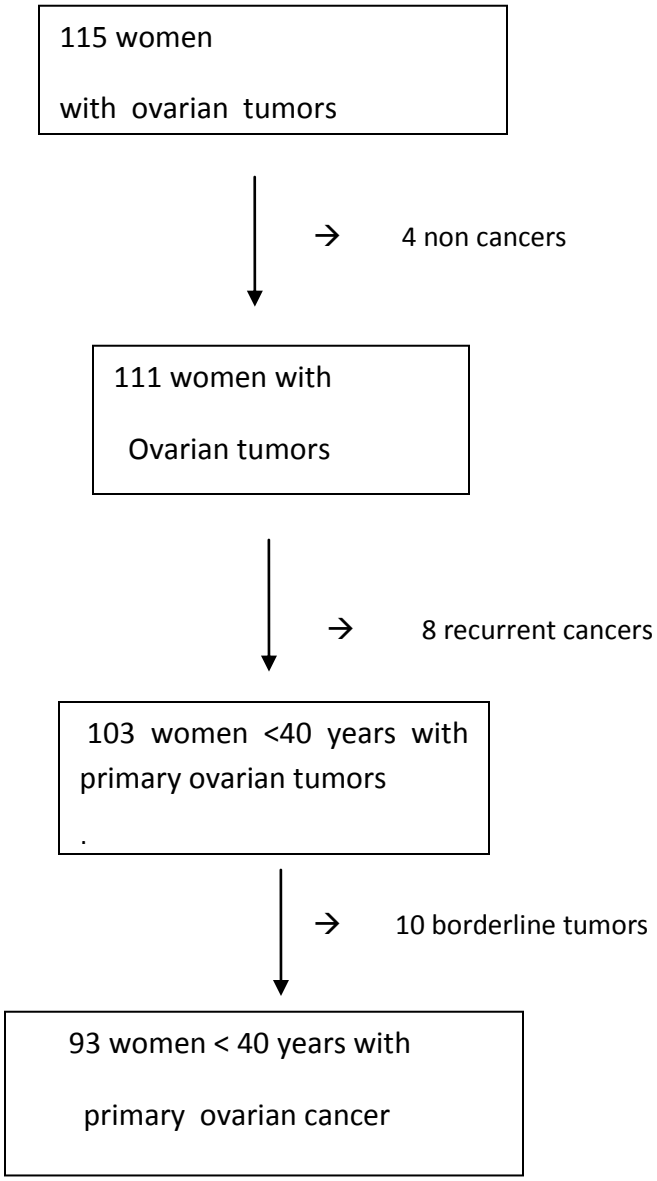
This study was approved by the Research Committee and Insitutional Review Board (Ethics Committee) of Christian Medical College, Vellore.

Settings: This study was conducted in the Department of Obstetrics & Gynecology , Christian Medical College Hospital, Vellore. Patients with histologically proven ovarian cancer who were treated from 1st January 2008- 31st December 2012 were retrospectively recruited for this study. The patients with ovarian cancer who were surgically treated during this period were identified through the electronic medical records. The Medical Records Department was able to come up with the list of all the patients treated in the 5 year period by using a computer software which was fed with a disease code number of C65 according to the WHO International Classification of Diseases-10 version 2012 (volume 3). All the patients fulfilling our inclusion criteria were collected, and those who had not come for follow-up were contacted by phone and those without contact telephone number were written to and were asked to contact us by phone or letter and were also asked to come for review in 2014. Mostly oral consent was obtained to include the patient for study, and written consent was taken if they attended clinic. If patient had expired, the details of death was obtained from a relative. The patient's demographic details, clinical presentations, histological features, treatments and survival outcome data were collected mainly by reviewing the charts, laboratory and radiological records stored in the electronic medical records. When necessary, inpatient and outpatient paper charts maintained in the Medical Records Department were studied. Other information pertaining to the study was

obtained through telephonic interview with patient or relatives after getting their consent. Data was analyzed using SPSS software.

Study Design: This was a hybrid of a retrospective and prospective design. Survival analysis was done for the primary outcomes and a cohort design was used for assessing risk factors.

FIGURE :2 Flow chart of patient recruitment



Inclusion Criteria: Patients with all of the features below were selected.

1. Patients ≤ 40 years with histologically proven ovarian cancer
2. Operated in CMC Vellore between January 2008 and December 2012.
3. Primary ovarian cancers

Exclusion Criteria: Patients with any of the features below were excluded.

1. Patients above age 40 years
2. Those who did not have cancer ovary on final histopathology
3. Patients who were treated with chemotherapy only and not operated.
4. Those who were operated elsewhere
5. Those who had ovarian tumors secondary to cancers from other organs

Primary outcomes : Survival and recurrence pattern and of women 40 years and below with ovarian cancer treated in our institution from January 2008 to December 2012

1. Death and time to death
2. Recurrence of cancer and time to recurrence

Secondary outcomes :

1. Complications of treatment
2. Pregnancy
3. Risk factors for death and recurrence

Sample size: With 90 % expected survival probability, 95% confidence interval and 7.5 % precision, the calculated sample was 72. The hazard ratio was calculated based on the difference in survival probabilities in the two group, the power of the study was kept at 80%, with alpha error kept at 5% (2 sided alpha).

Statistical Analysis: Descriptive statistics were obtained for all variables. Continuous variables which were normally distributed were expressed using mean and standard deviation; non-normal continuous variables were expressed using median and range. For categorical variables count and percentages were given, and for comparing two categorical variables crosstabs with chi-square statistics were obtained. Kaplan-Meir estimation method was used to get the estimates of mean survival and recurrence time. Tarone-Ware test was applied to check the significance of difference between two groups. Statistical analysis was carried out using SPSS version 20.

RESULTS

115 patients were retrospectively enlisted for our study out of which 93 could fulfil our inclusion criteria.

Table 7. Year of surgery

Year	Number of Patients
2008	31
2009	28
2010	12
2011	24
2012	20

Table 8. Place Distribution

	Number of patients	Percent (%)
Vellore	22	19.1
Rest of Tamil Nadu	10	8.7
Rest of India	75	65.2
Outside India	7	6.1

Majority of our patients were coming from outside Tamil Nadu state.

Table 9. Histological Distribution of the study patients

Histiopathological pathological classification (n=111)	Frequency	Percent	Notes
Epithelial	79/111	71	
Serous	31	28	2 with sarcomatous changes
Mucinous	23	21	2intestinal Subtypes
Endometrioid	11	10	
Cell Clear	2	1.8	
Not specified	2	1.8	
Non epithelial	32	29	
Germ cell tumours	21	18.9	
Mixed GCT	9	8.1	
Immature teratoma	5	4.5	
Yolk sac	4	3.6	
Dysgerminoma	3	2.7	
Sex cord stromal	7	6.3	
Granulosa	3	2.2	
sertoli-leydic	2	1.8	
Gynanroblastoma	1	0.9	
Androgen secreting tumor	1	0.9	
Others	4	3.6	
Metastatic	2	1.8	
Hemangio-endothelioma	1	0.9	
Granulocytic sarcoma	1	0.9	
Borderline	10	9	4 serous,6mucinous
Note: Description done on the initial 111 patient with ovarian tumor.			

Looking at the 111 patient with ovarian tumor 79(71.1%) patients had epithelial tumour, with the following cell types: serous 31, mucinous 23, endometrioid 11, clear cell 2 and adenocarcinoma not otherwise specified 2.

Of the 111 ovarian tumours, 10 were borderline tumors (9 %); 4 of these were serous and 6 were mucinous. There were a total of 7 sex cord stromal tumors (6.3%): 3 granulosa cell tumors, 2 sertoli leydig cells, one gynandroblastoma an one androgen secreting tumor that was not otherwise specified. There were a total of 21 germ cell tumors (18.9%): 9 were mixed germ cell tumors, 5 immature teratoma , 4 yolk sac, and 3 dysgerminoma,

There were two metastatic tumors, and two other tumors namely a granulocytic sarcoma and a Hemangioendothelioma.

The median age of the patients was 32 years with a range of 13 to 40.

Table 10. BMI

Variable	N	Mean (S.D)
BMI	85	22.5(5.4)

BMI	FREG	Percent
Under weight <18.50	22	25.9
Norma 18.5-24.99	35	41.2
Obese > 30	21	24.7
Severely obese > 40	7	8.2
Total	85	100.0

Perfomance status of a patient has prognostic value as with residual disease after surgery and volume of ascites. Of the 93, performance status was documented for 87 patients, 36 of them had ECOG of 0, 45 with ECOG 1 , 5 with ECOG of 2 and I with ECOG 3.

Table 11. Performance status Distribution

Performance status	Frequency	Percent
0	36	41.38
1	45	51.72
2	5	5.75
3	1	1.15
Total	87	100

Most patients were of parity 2 or less as shown in Table 12.

Table 12. Parity of the patients

Parity	Frequency	Percent %
0	31	33.3
1	27	29.0
2	27	29.0
3	5	5.4
4	2	2.2
6	1	1.1
Total	93	100

Regarding oral contraceptive use we could get information on only 46 patients out of which 9 (19.6%) gave history of its use and 37(80.4%) did not.

Table 13. Oral contraceptive use

Oral Contraceptive use	Frequency	Percent (%)
Yes	9	19.6
No	37	80.0
Total	46	100

Of the presenting symptoms we could get information for 91 of the 93 patients , 2(2.2%) had dyspepsia as the presenting symptom, 26(28.6%) complained of distension of abdomen , majority of the patient 44(47.2% came with complaints of pain, 20 had other symptoms like

To elaborate on the other symptoms , about 10 presented with menstrual symptoms ranging from secondary amenorrhea to menorrhagia,in fact one patient had polymenorrhea for which oral contraceptive was given for almost a year till the diagnosis of ovarian tumor was made. one patient had amenorrhea with virilization and another complained of voice change ;deepening of voice with hirsutism, there were 8 incidental findings ,3 at the time of caesarean sections, one at the time of diagnostic laparoscopy for infertility and one at the time of abdominal puerperium sterilization , and two during an early pregnancy scan, there were few who presented with feeling of mass in the abdomen,and other symptoms like backache, pedal edema,constipation, bleeding from rectum with sensation of incomplete evacuation , and urinary symptom of pain during micturition and one patient presented with pain in the gluteal region which turned out to be a granulosa cell tumor.

Table 14. Clinical presentation distribution

Presentation	Frequency	Percent (%)
Dyspepsia	2	2.2
Distension	26	28.6
Pain	43	47.2
Other	20	22.0
Total	91	100

Table 15. Tumour markers

Variables	n	Median(min,Max
CA 125	82	92.2(2,19100)
hCG	35	1 (0.1,6142)
AFP	36	6.3 (0.5,496274)
LDH	35	609 (67.3,17400)
Serum Albumin	63	Mean (S.D) 3.97(0.72)

Table 16. Biomarkers

CA125	Freq.	Percent (%)
<200	54	65.9
>200	28	34.1
Total	82	100.0

hCG	Freq.	Percent (%)
<5	21	60.0
>5	14	40.0
Total	35	100.0

AFP	Freq.	Percent (%)
<5.5	18	50.0
>5.5	18	50.0
Total	36	100.0

LDH	Freq.	Percent (%)
<460	11	31.4
>460	24	68.6
Total	35	100.0

Serum Albumin	Freq.	Percent (%)
<3.3	12	19.1
>3.4	51	80.9
Total	63	100.0

Serum assay of CA 125 for 82 patients ,HCG for 35,AFP for 36, LDH for 35 , and serum Albumin for 63 was done , and of the 93 patients with serum CA125 28 patients had assay >200 U/Ml,d of the 35 who had HCG assay 14 had values >5 and of the 36 patients with serum AFP assay ,18 had values >5.5 and of the patient with pre-operative serum Albumin ,of the 63, 12 had serum albumin less than 3.3 mg/dl.

Table 17. Primary treatment distribution:

Primary Treatment	Frequency	Percent
Surgery	72	77.4
Chemo	21	22.6
Total	93	22.6

Surgical staging was done according to FIGO (International Federation of Gynecology and Obstetrics) 1988. 47 of the 93 were staged as Early (from stage 1a to stage 2c) and 46 patients were staged as advanced stage from stage 3a to stage 4) .

Table 18. Stage distribution

Stages	Freq.	Percent
Early stage	47	50.5
Advanced stage	46	49.5
Total	93	100

Table 19. Complexity of surgery distribution

Complexity of surgery	Frequency	Percent %
Simple	21	22.6
Intermediate	69	74.2
Complex	3	3.2
Total	93	100

Surgery for most patients was of intermediate complexity as sown in Table 19.

Regarding optimal cytoreduction or surgical clearance , 53 of the 93 had no gross residual tumor ,15 had less than 1 cm residual (optimal cytoreduction) , 19 had > 1 cm residual and three had open laparotomy with biopsy .

Table 20. Surgical clearance

Surgical Clearance	Frequency	Percent %
No gross residual	56	60.2
Less than 1 cm Residual	15	16.1
More than 1 cm Residual	19	20.4
Biopsy only	3	3.2
Total	93	100

Fertility sparing surgery was done in 23 patients (27%). It was found out that three of our patients had become pregnant and had given birth.

Table 21 . Fertility sparing surgery distribution

Uterus	Frequency	Percent %
Removed	63	73
Not Removed	23	27
Total	86	100

Regarding the complication of surgery nobody died intra-operatively nor within 28 days of surgery of the 115 operated. The commonest complication was post-operative fever with 21 patients out of 115 having it. Five patients a woun problems that included one with burst abdomen. Paralytic ileus was seen in one patient, spinal headache in one, ureteric injury in one and underwent uretero-neocystectomy. One had parastomal abscess and prolapse of the colostomy. Relaparatomy was required in one patient with hemoperitoneum : this was a case of mucinous adenocarcinoma who underwent total abdominal hysterectomy with bilateral salpingo-oopherectomy with omentectomy and appendectomy.

Table 22. Complications of surgery

COMPLICATION	N	PERCENT
Fever	21	19
Paralytic ileus	1	0.9
Thromboembolism	0	0
Others	7	6.3

Majority of our postoperative cases did not have complications.

Table 23. Tumour Types distribution

Tumor	Frequency	Percent %
Epithelial tumour	64	69.6
Non-epithelial tumour	28	30.4
Total	92	100

Table 24. Histological type distribution

Histology	Frequency	Percent
Epithelial	64	68.8
Sex cord Stromal	4	4.3
Germ cell	21	22.6
Other	4	3.2
Total	93	100

Other includes: 1. Granulocytic sarcoma of ovary 2. Hemangoepithelioma

For secondary treatment of the disease 5 had surgery,23 had chemotherapy, I had radiotherapy, 1 (androgen secreting tumor) , and 31 patients did not have secondary treatment with us.

Table 25. Grade of tumour

Grade	Frequency	Percent%
Well Differentiated	15	16.1
Moderate	13	14.0
Poor	21	22.6
Not described	44*	47.3
Total	93	100

*Many serous tumours did not have grading as they are assumed to be high grade by its very nature. Sex cord and germ cells tumours are usually not graded .

Table 26. Secondary treatment distribution

Secondary treatment	Freq.	Percent (%)
Surgery	5	8.2
Chemotherapy	23	37.7
Radiotherapy	1	1.6
Other	1	1.6
None	31	50.8
Total	61	100

A significant number of our patients could not afford secondary treatment.

Table 27. Recurrence Distribution

Recurrence	Freq.	Percent (%)
Yes	29	37.7
No	48	62.3
Total	77	100

The mean recurrence rate was 38%

There were 76 patients on whom survival and progression free time was calculated, and out of the 76 patients there were total of 10 deaths during our follow period with an estimate mean survival time of 5.4 years with standard error of .239 years(95%CI 4.971-5.908).66 (87 %) patients were censored mainly for two reasons ,first reason being that quite a number of our patients(14 of them) survival was known up to certain time after the surgery followed by loss of contact , this year 2014 we were sure of 29 patients survival, there were 23 patients who were lost to follow-up after surgery.

Table 28. Survival distribution

Survival status	Freq.	Percent (%)
Alive	66	86.8
Dead	10	13.2
Total	76	100

Table 29. Survival and recurrence based on tumor types

Tumour	Survival status		Total	Recurrence		Total
	Alive	Dead		Yes	No	
Epithelial tumour	42	9	51	23	29	52
Non-epithelial tumour	23	1	24	5	19	24
Total	65	10	75	28	48	76

9 of the patients in epithelial group and 1 in the non epithelial group died during follow up

Table 30. Survival based on stage of the disease

Stages	Epithelial tumour			Non-epithelial tumour		
	Survival status		Total	Survival status		Total
	Alive	Dead		Alive	Dead	
Early stage	23	0	23	15	0	15
Advanced stage	19	9	28	8	1	9
Total	42	9	51	23	1	24

Patient with Early stage disease survival rate was 100%

Table 31. Recurrence based on tumor types and stages

Stages	Epithelial tumor			Non-Epithelial tumor		
	Recurrence status		Total	Recurrence status		Total
	Yes	No		Yes	No	
Early stage	0	23	23	3	12	15
Advanced stage	23	6	29	2	7	9
Total	23	29	52	5	19	24

Table. 32 Survival and recurrence state based on primary treatment

Primary treatment	Survival status		Total	Recurrence status		Total
	Alive	Dead		Yes	No	
Surgery	57	3	60	16	44	60
Chemo	9	7	16	13	4	17
Total	66	10	76	29	48	77

Survival in the primary chemotherapy treated group was poor, an recurrence was high

Table 33. Time to death

Dead		Censored		Mean Survival time			
Total No. of Patients	No. of Events	Total No. of Patients	%	Estimate	Std. Error	95% Confidence Interval	
						Lower Bound	Upper Bound
76	10	66	86.8%	5.439	.239	4.971	5.908

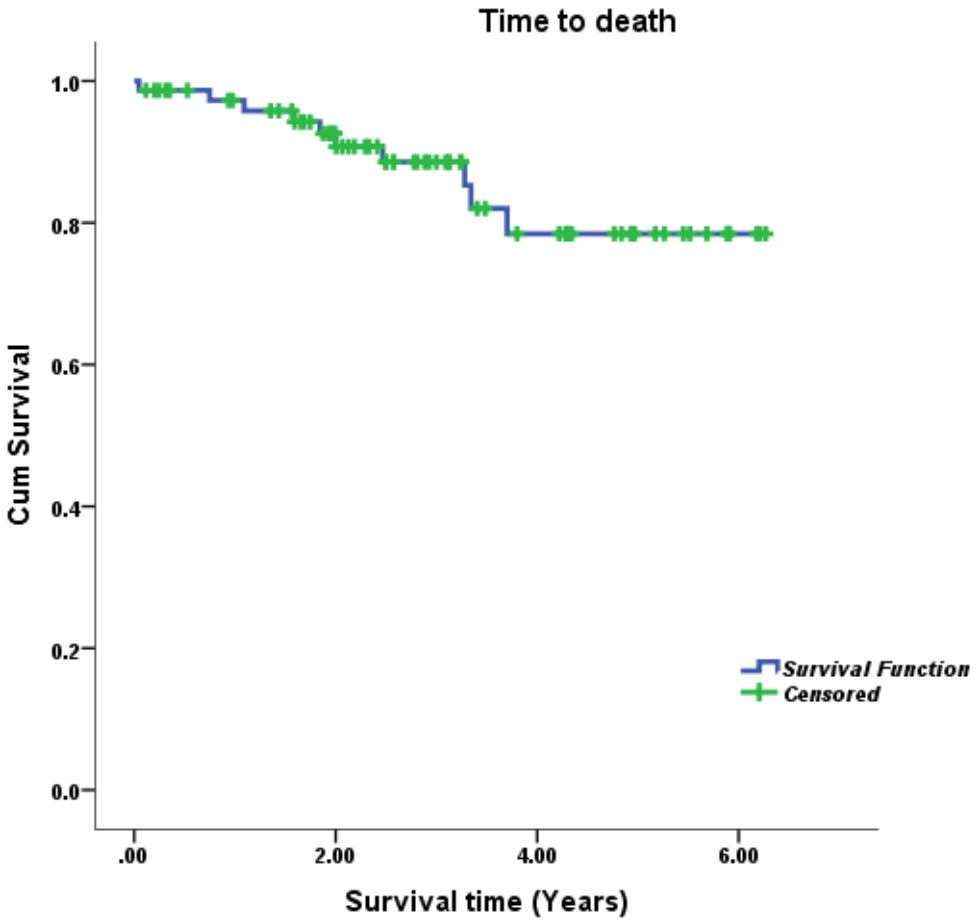


Figure 3. Overall survival

Table 34. Time to recurrence

Dead		Censored		Mean Recurrence time			
Total No. of Patients	No. of Events	Total No. of Patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval	
						Lower Bound	Upper Bound
76	28	48	63.2%	4.261	.295	3.682	4.840

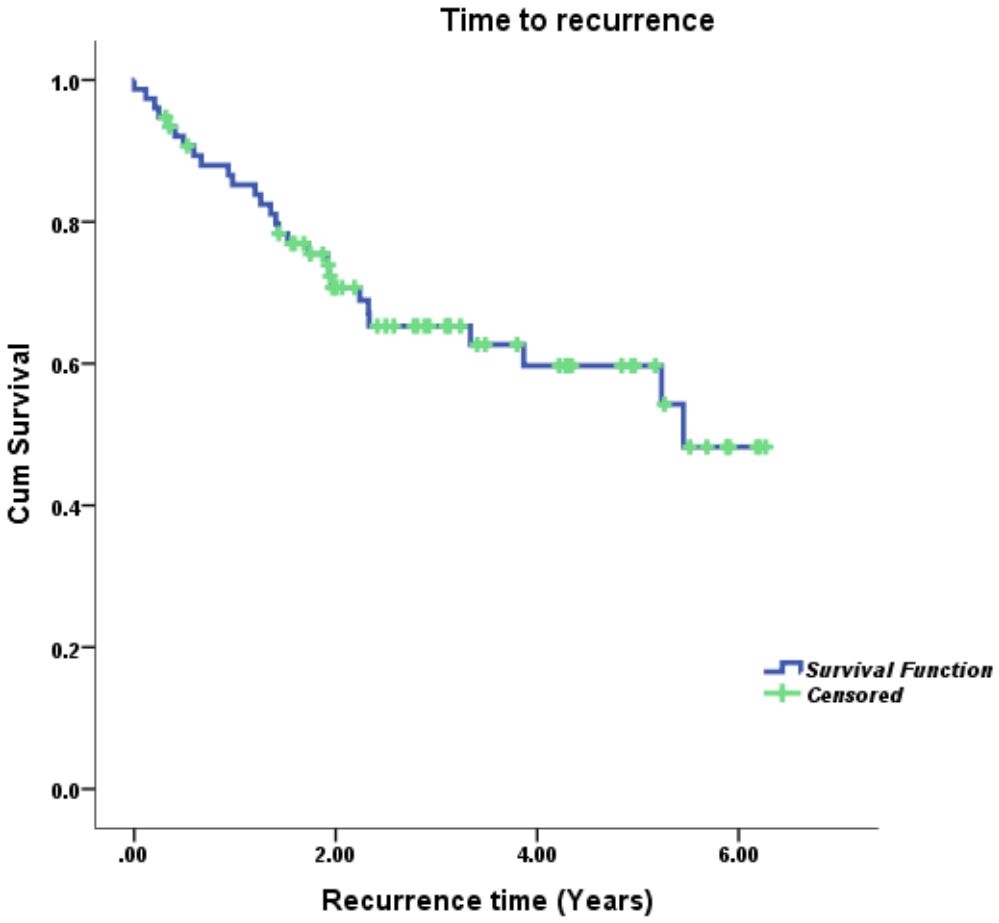


Figure 4. Overall Progression Free Survival

Table 36. Time to Death by histology (Epithelial Vs Non Epithelial tumors)

Tumours	Total No of Patients	Total No of Events	Censored		Mean Survival time				Sig[a]
			Total No of Patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Epithelial	51	9	42	82.4%	5.000	.347	4.319	5.681	0.100
Non Epithelial	24	1	23	95.8%	6.028	.235	5.568	6.489	
Overall	75	10	65	86.7%	5.431	.241	4.958	5.903	

As for **comparison of survival time for epithelial and non epithelial tumors**, we had total number of 51 patients in the epithelial group and 24 patients in the non epithelial group with a mean survival time of 5 years (95 % confidence interval 4.3 to 5.7), and for the non epithelial group with mean survival time of 6 years with 95% confidence interval(5.6 to 6.5); 9 patients from the epithelial group have died and one from non epithelial group (this was a case of hemangio–endothelioma of the ovary). There was no statistically significant difference in overall survival by histology.

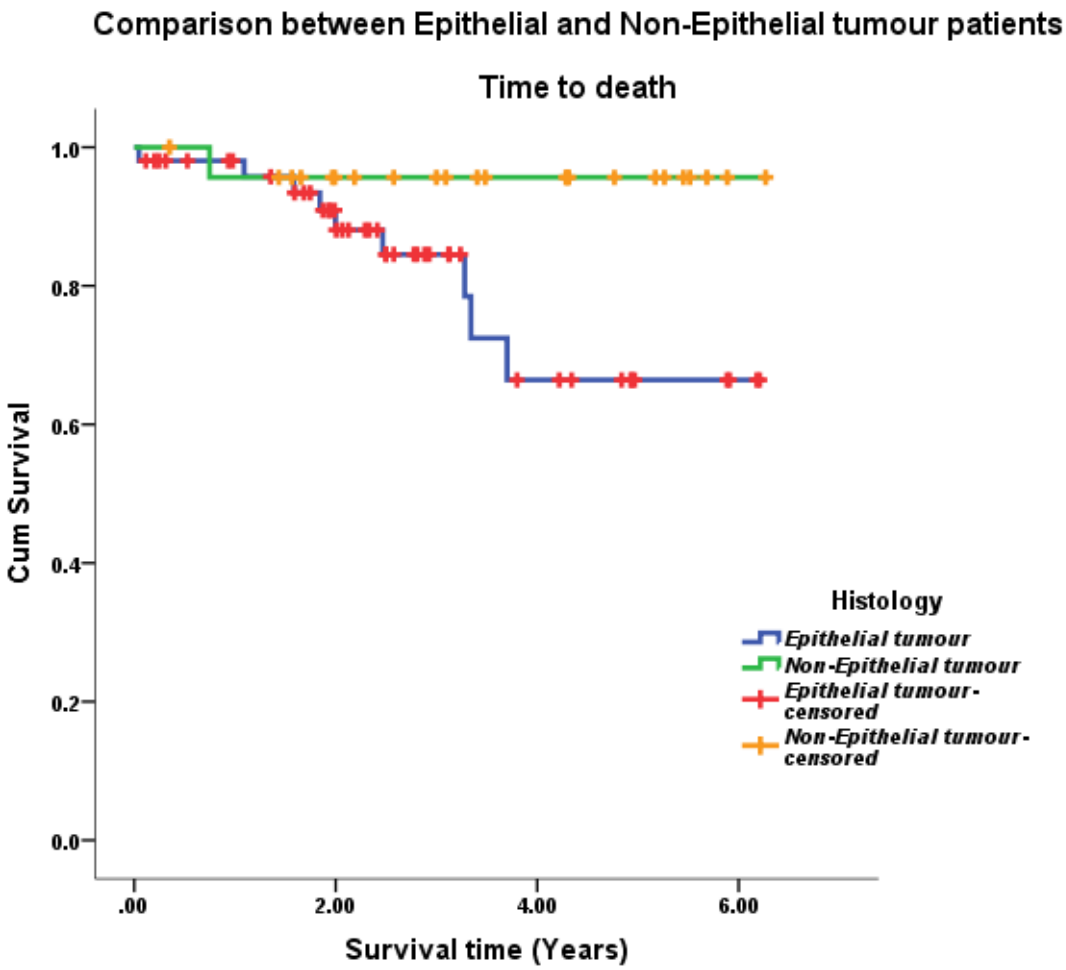


Figure:5 Overall survival by histology

Table 37. Time to Recurrence by histology

Tumours	Total No of Patients	Total No of Events	Censored		Mean Recurrence time				Sig[a]
			Total No of Patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Epithelial	51	22	29	56.9%	3.799	.378	3.058	4.539	0.022
Non Epithelial	24	5	19	79.2%	5.315	.389	4.553	6.078	
Overall	75	27	48	64.0%	4.304	.297	3.722	4.886	

a. Significance is calculated using Tarone-Ware test.

The time to recurrence for epithelial tumors was 3.8 years (95 % CI 3.1 to 4.5) an for nonepithelial tumors it was 5.3 years (95 % CI 3.7 to 4.9). This was statistically significant (p=0.022).

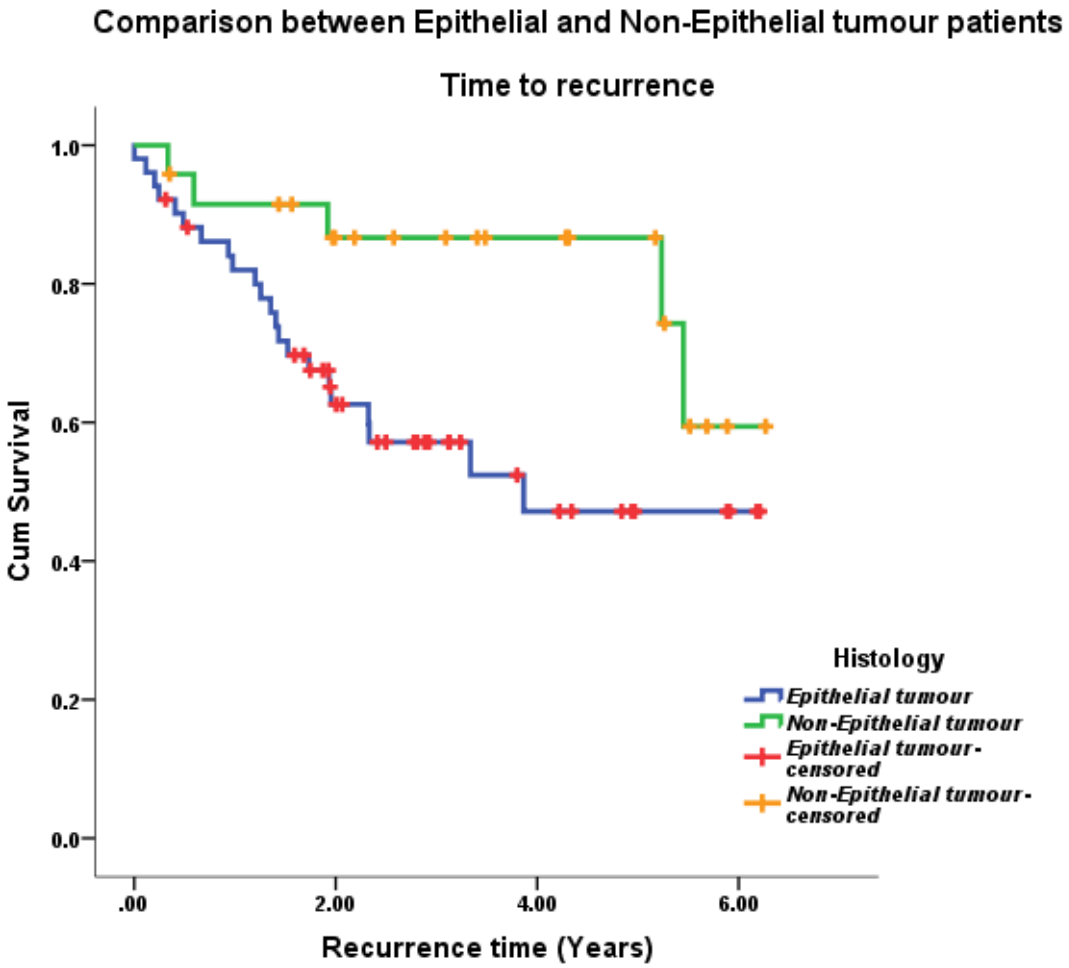


Figure 5. Progression Free Survival by histology

Table 38. Time to Death by primary treatment (Surgery Vs Chemotherapy)

Treatment Group	Total No of patients	Total No of Events	Censored		Mean survival time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Surgery	60	3	57	95.0%	5.945	.183	5.587	6.302	<0.001
Chemo	16	7	9	56.3%	3.641	.555	2.554	4.728	
Overall	76	10	66	86.8%	5.439	.239	4.971	5.908	

a. Significance is calculated using Tarone-Ware test.

The mean overall survival time of for primary surgery was 6 years (95 % C.I 5.6 to 6.3) and 3.6 years (95% CI 2.2 to 4.7) years for chemotherapy. Tis was statistically significant ($p<0.001$).

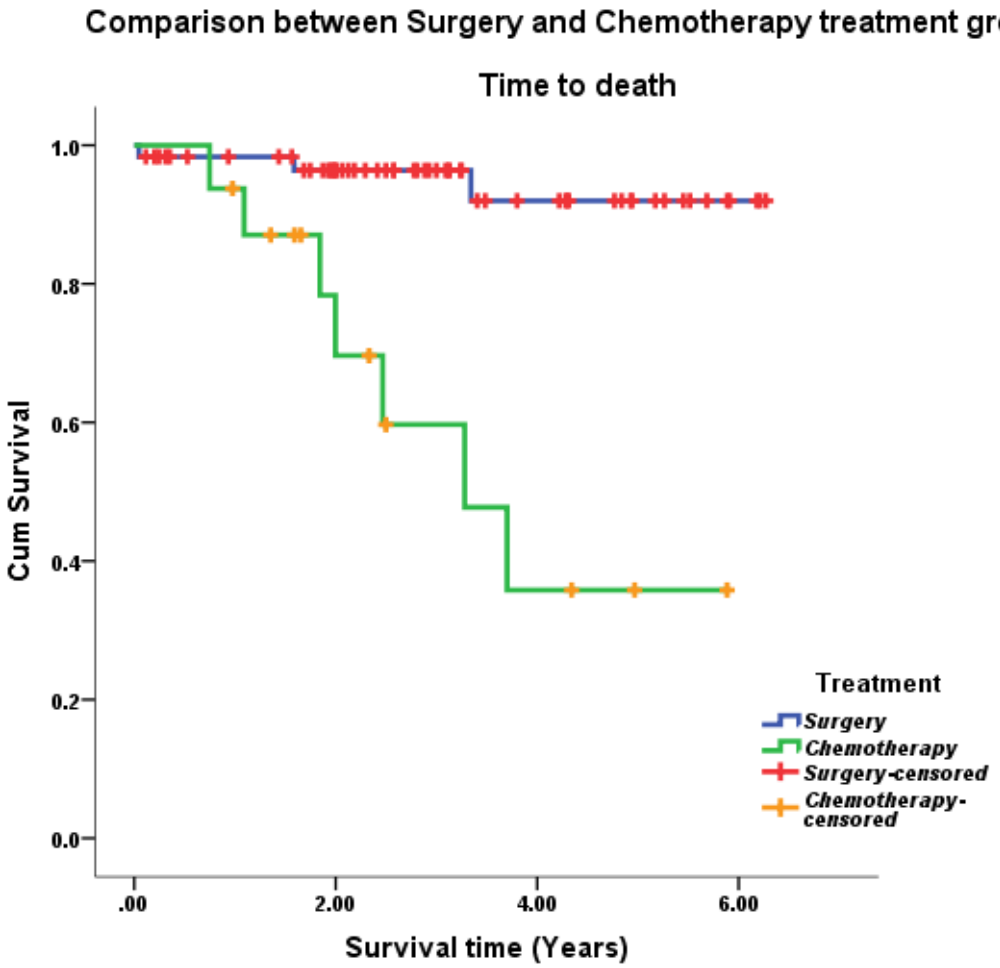


Figure 6. Overall survival by primary treatment

Table 39. Time to recurrence

Treatment Group	Total No of patients	Total No of Events	Censored		Mean Recurrence time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Surgery	60	16	44	73.3%	4.809	.306	4.209	5.408	<0.001
Chemo	16	12	4	25.0%	2.246	.517	1.233	3.259	
Overall	76	28	48	63.2%	4.261	.295	3.682	4.840	

a. Significance is calculated using Tarone-Ware test.

The mean time to recurrence after primary surgery was 4.8 years (95 % CI 4.2 to 5.4) and for neoajuvant chemotherapy it was 2.3 years (95 % CI 1.2 to 3.3). This was also statistically significant ($p<0.001$).

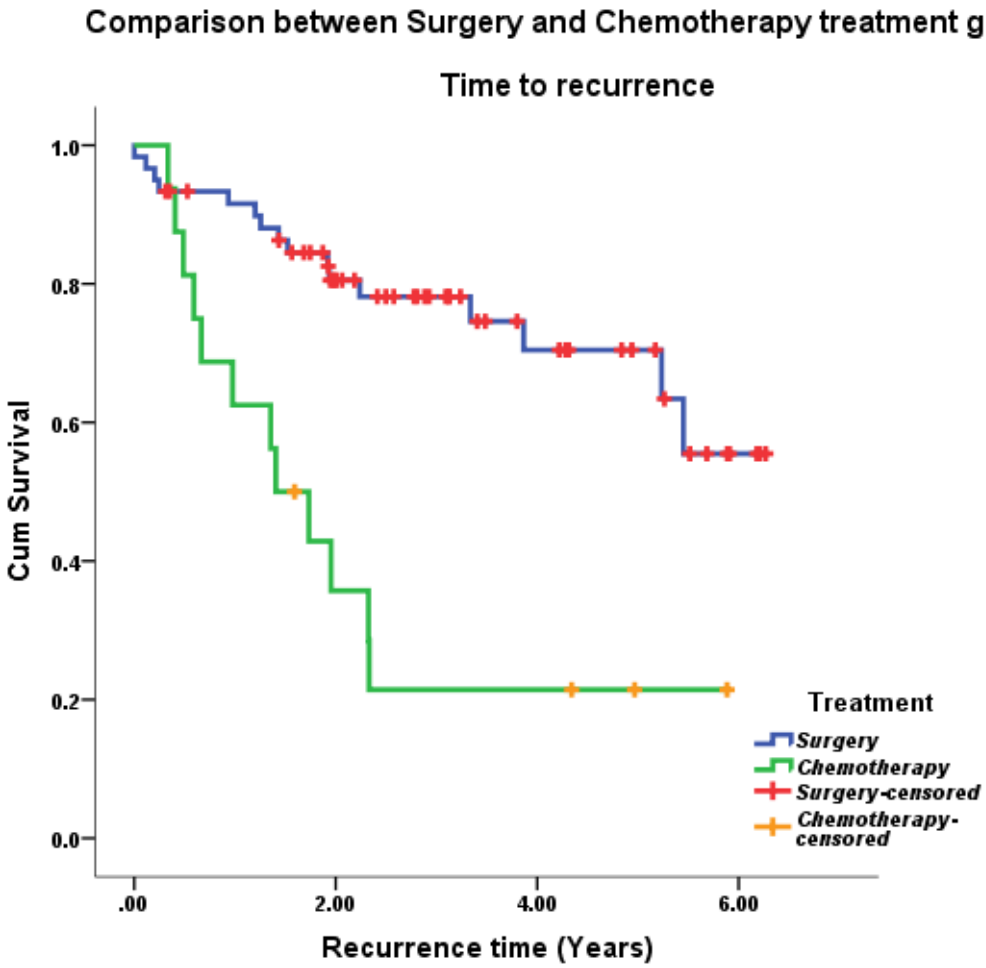


Figure 7. Progression free survival by primary treatment

Table 40. Time to death by Stage of disease (Early vs Advanced)

Stages	Total No of patients	Total No of Events	Censored		Mean survival time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Early stage	38	0	38	100.0%	Can't be calculated because in early stage group every patients were censored, i.e no events occurred.				-
Advanced stage	38	10	28	73.7%					
Overall	76	10	66	86.8%					

Time to Death by stage of cancer could not be done as all the 38 patients in the early stage had all survived up to the follow up time. Of the advanced group, 10 out of the 38 had died.

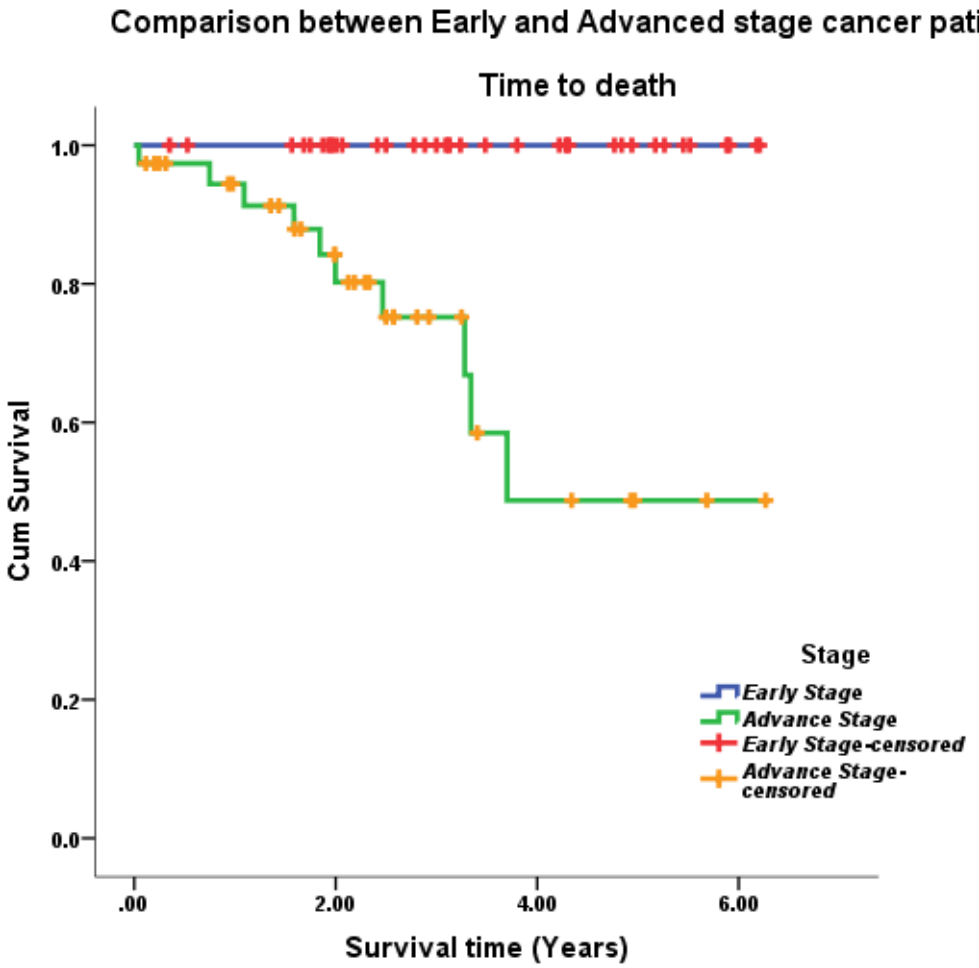


Figure 8. Overall survival by Stage of disease

There is a clear difference in survival curves between early and late stage disease.

Table 41. Time to Recurrence by Stage of disease

Stages	Total No of patients	Total No of Events	Censored		Mean survival time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Early stage	38	3	35	92.1%	5.877	.176	5.532	6.221	<0.001
Advanced stage	38	25	13	34.2%	2.651	.398	1.872	3.430	
Overall	76	28	48	63.2%	4.261	.295	3.682	4.840	

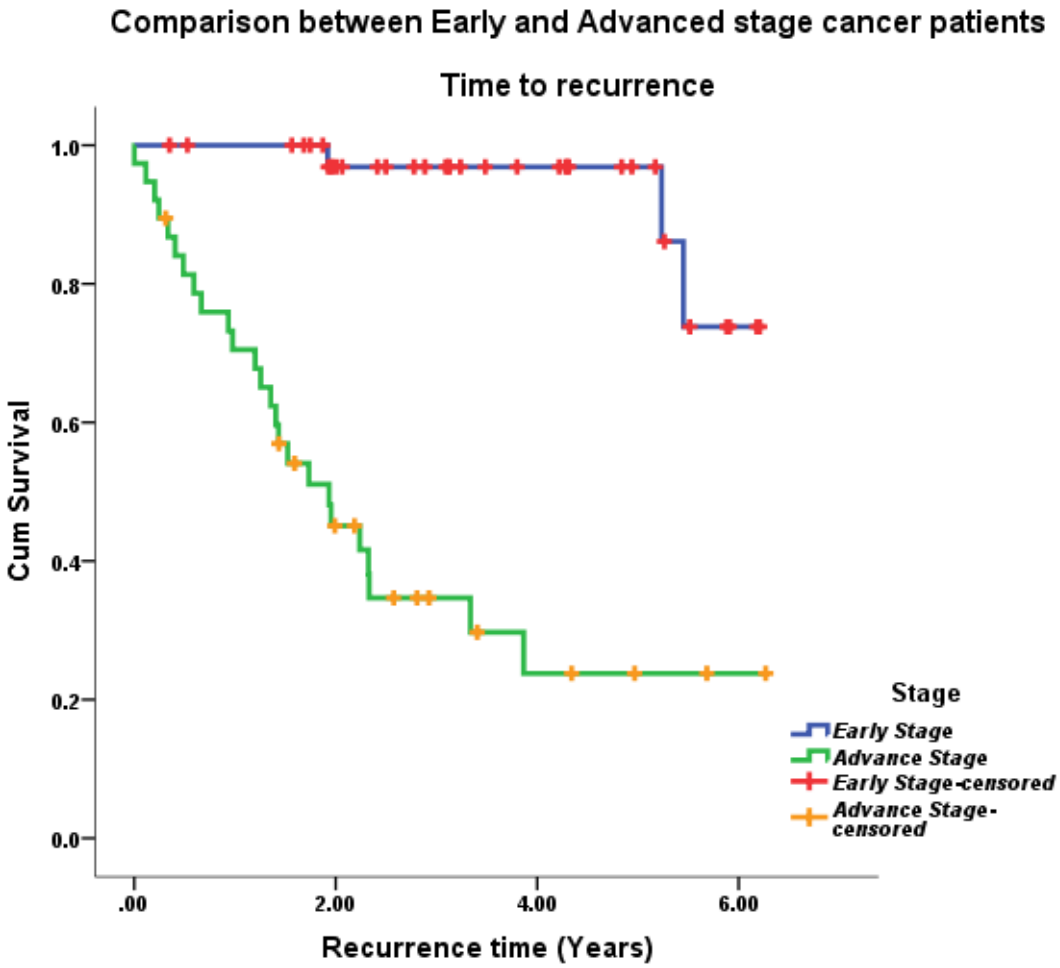


Figure 9. Progression Free Survival by stage of disease

There was a statistically significant difference in time to recurrence between patients with early stage disease and advanced stage disease ($p<0.001$).

Table: 44 Cytoreduction (Optimal Vs Sub-Optimal)

Time to death

Cytoreduction	Total No of patients	Total No of Events	Censored		Mean survival time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Optimal cytoreduction	59	5	54	91.50%	5.73	0.20	5.34	6.13	0.003
Sub-optimal cytoreduction	17	5	12	70.60%	3.67	0.72	2.25	5.09	
Overall	76	10	66	86.80%	5.44	0.24	4.97	5.91	

a. Significance is calculated using Tarone-Ware test.

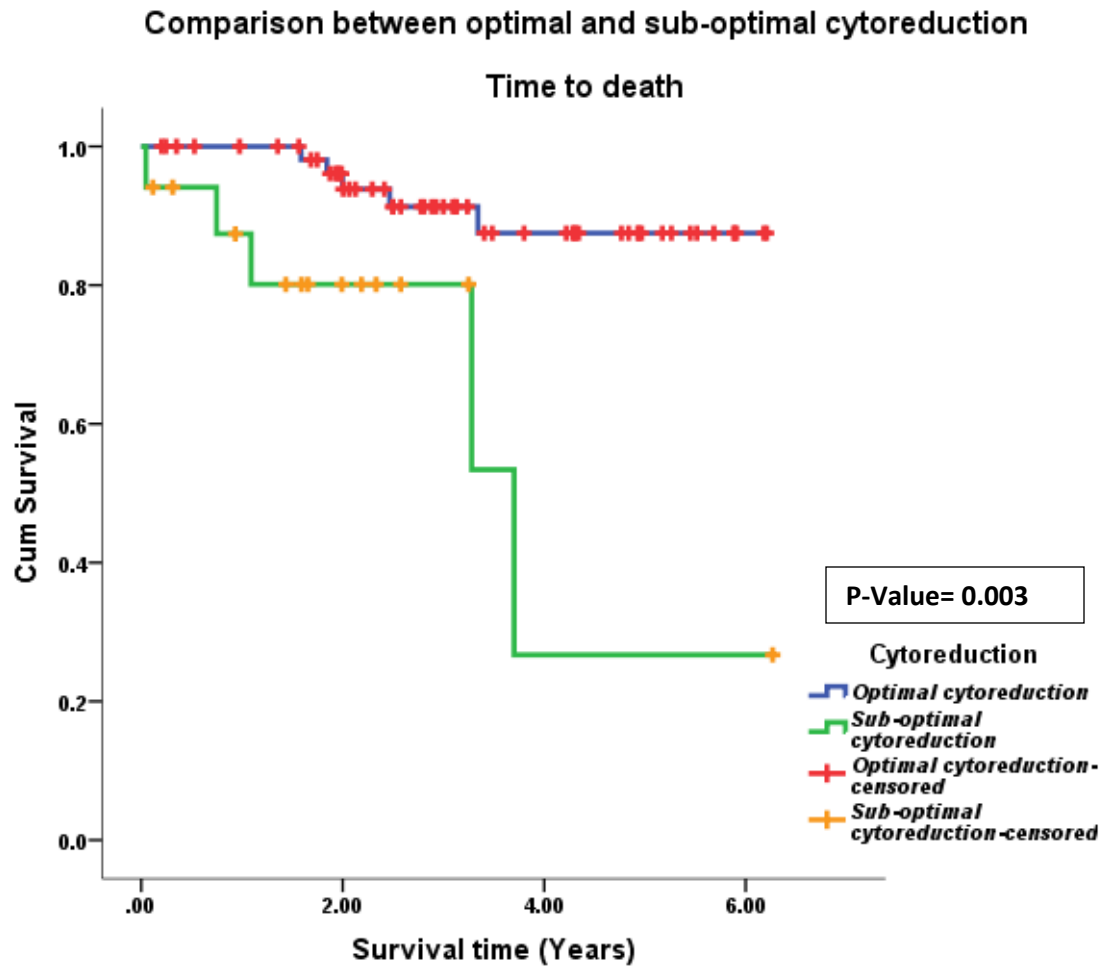


Figure:11

Table: 45 Time to recurrence

Cytoreduction	Total No of patients	Total No of Events	Censored		Mean survival time				Sig[a]
			Total No of patients	Percent (%)	Estimate	Std. Error	95% Confidence Interval		
							Lower Bound	Upper Bound	
Optimal cytoreduction	59	18	41	69.50%	4.66	0.30	4.07	5.25	0.002
Sub-optimal cytoreduction	17	10	7	41.20%	2.43	0.64	1.18	3.68	
Overall	76	28	48	63.20%	4.26	0.30	3.68	4.84	

a. Significance is calculated using Tarone-Ware test.

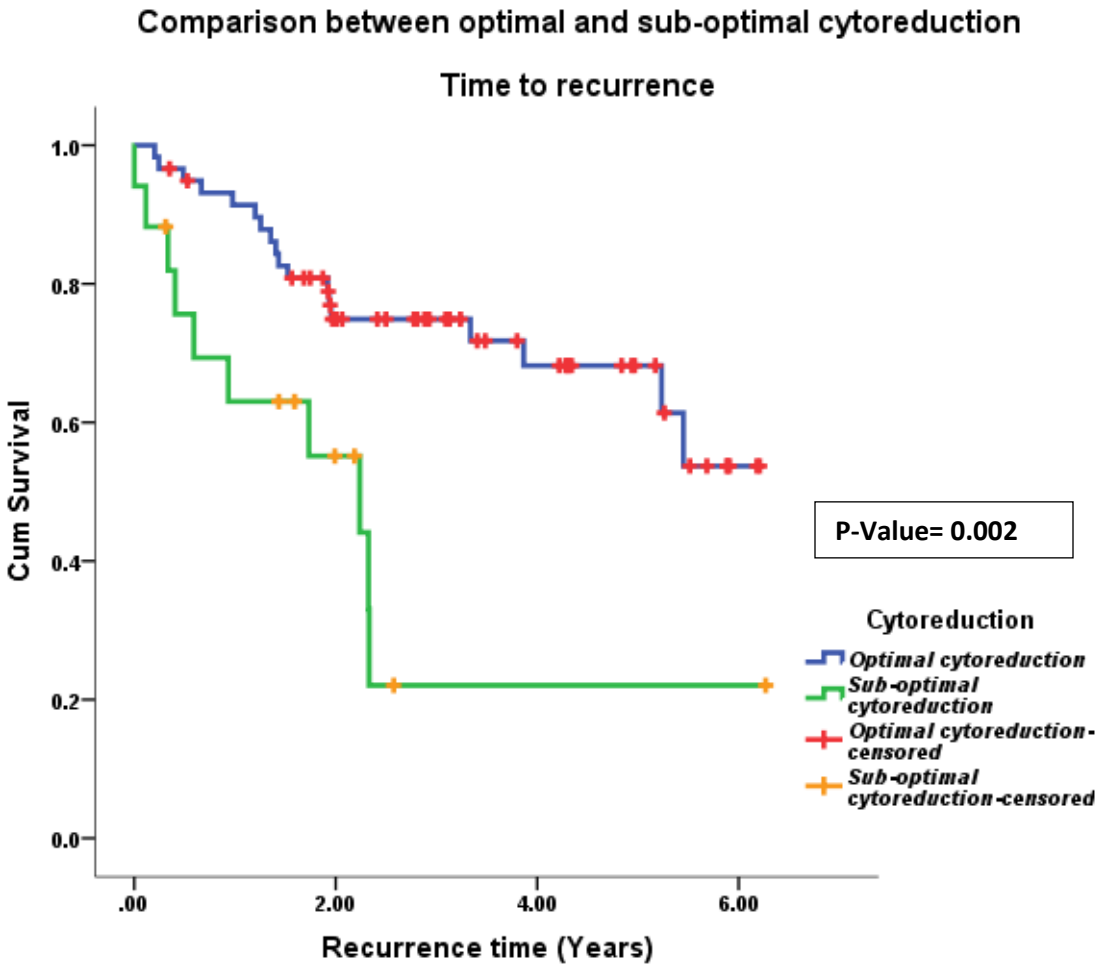


Figure: **Tables: 46**

Table 42: Univariate and multivariate Cox regression analyses of potential risk factors affecting survival of ovarian cancer patients after surgery

Factors	N	Survival status		Unadjusted (Univariate)		Adjusted (Multivariate)	
		Dead (n)	Alive (n)	HR (95% C.I)	P-value	HR (95% C.I)	P-value
Histology							
Non-Epithelial Tumour	24	1	23	1	0.10	1	0.49
Epithelial tumour	51	9	42	5.81 (0.73-46.22)		2.22 (0.23-21.34)	
Treatment							
Surgery	60	3	57	1	<0.001	1	0.25
Chemotherapy	16	7	9	10.17 (2.62-39.4)		2.42 (0.54-10.64)	

Only type of primary treatment was significant for overall survival. Those who had primary chemotherapy were 10 times more likely to die as compared to those who had primary surgery.

Table 43: Univaritate and Multivariate Cox Regression analyses of potential risk factors for recurrence of ovarian cancer after surgery

Variables	N	Recurrence status		Unadjusted (Univariate)		Adjusted (Multivariate)	
		Yes (n)	No (n)	HR (95% C.I)	P-value	HR (95% C.I)	P-value
Histology							
Non-Epithelial	24	5	19	1		1	
					0.05		0.15
Epithelial	52	23	29	2.7 (1.02-7.30)		2.36 (0.74-7.51)	
Treatment							
Surgery	60	16	44	1		1	
					<0.001		0.42
Chemotherapy	17	13	4	4.3 (2.01-9.31)		1.44 (0.60-3.48)	
Stages							
Early stage	38	3	35	1		1	
					<0.001		<0.001
Advance stage	39	26	13	14.1 (4.21-47.4)		12.6(3.49-45.49)	

Epithelial histology, primary chemotherapy and advance stage at presentation were significant adverse factors on univariate analysis. In multivariate analysis the only independent risk factor for recurrence was stage of disease.The hazard ratio for recurrence in advanced stages was 12.6(95% CI3.5 to45.5 p<0.001)

DISCUSSION

Cancer of the ovary is the most fatal of all female gynecological cancers. Worldwide, it is the 7th most common cause of death in the female. In India, it is the third most common cancer affecting women, next to cancer of the breast and cervix. Although most of the literature combines clinical features and treatment of epithelial and non-epithelial tumors, these need to be studied separately. It is also not clear how often epithelial tumors effect young women and whether the bi-modal age distribution clearly separates out epithelial and non epithelial tumors, hence the aim and objective of this study was to evaluate the clinico-pathological features and survival outcome of women 40 years and younger with ovarian cancer treated at a tertiary care hospital in India.

Most of the studies from India on ovarian cancer are case reports or clinicopathological studies. There are no survival studies done in the below 40 year age group, especially for epithelial ovarian cancer.

In our study we were able to follow up 76 patients out of 93 (82 %). In spite of trying to contact patients and their relatives by letters, phone calls and email, 18 % of patients were lost to follow up. This is a common problem in our country where patients default due to ignorance and poverty. Access to cancer care is limited and often patients have to travel long distances. Cancer hospitals are also ill equipped to contact patients who default or arrange financial help for the poor.

Time to death and time to recurrence could be calculated in the 76 patients. There were a total of 10 deaths during our follow period with an estimated mean survival time of 5.4 years with a 95% confidence interval of 4.97 to 5.91. There were no peri-operative deaths. Of the 28 cases who had recurrence of disease 10 went on to die. All those who died had stage III or IV disease; 5 had serous adenocarcinoma (grade 2 or 3), 2 had endometrioid type , 1 with mucinous, and one with non specified adenocarcinoma. The only death from the non-epithelial group was a rare type of ovarian cancer, a hemangi-endothelioma. We could not show a significant difference in time to death between epithelial and non-epithelial tumours as the numbers wee small. The mean time to recurrence was 4.3 years (95% confidence interval 3.68 to 4.84). There was a statistically significant difference ($p=0.022$) in time to recurrence between epithelial (3.8 years) and non-epithelial tumours (5.3 years).

In our study, epithelail cancers were seen in 69%. The commonest histological type was serous cystadenocarcinoma(28%). Germ cell tumours constituted 23 % of cases.

In an Indian study done (16) a study to look at the histologic pattern, bilaterality and clinical evaluation of 957 ovarian neoplasm done over a period of 10 years in eastern India, in all age group, the most common histological type was serous cystadenoma (30%), followed by mature teratoma (16%) and mucinous cystadenoma (11%). As in our study, epithelial tumors formed 61% of their cases. Serous cystadenoma too was the most common malignant tumor. Most of their malignant tumors presented as stage III (60%). In the young women in our study, the commonest presentation was pain and 50 % were stage

I or II. In the study from east India, the overall survival rate was 85% for stage I tumor, 65% for stage II, 30 % for stage III, and 15.5 % for stage IV tumor. In our study, survival of the early stage cancer (stage I and II) showed 100% survival rate .whereas for advanced stage (Stage III and IV), the survival rate was 74% with overall survival rate of 87%.

A Chinese study on young women showed the commonest histologic type to be serous adenocarcinoma (56%). For stage IA disease, their 2 and 5 year survival was 86% and 82%.(55). They concluded their study by stating that women under 35 years with epithelial ovarian cancer mostly have serous adenocarcinoma with a good prognosis so such women could have fertlility preserving surgery.

Another study done in Japan (56) showed that mucinous ovarian cancer was the commonest tumor in young reproductive women .

A large study done over a period of 25 years showed that young age, good performance status, early stage, optimal cytoreduction and lower grade tumors were positive prognostic factors for survival (57). Another study on the effect of platinum based chemotherapy on survival, the 29 (out of 624) who were below 40 years showed a 5 year survival of 65% against the 20% among those above 70 years (13). There are several studies on survival among patients with malignant ovarian tumor (15) and all the results showed good survival outcome among those who were adequately treated by surgery and chemotherapy..

In our study, mean survival time of 6 years for surgery (95 % CI 5.6 to 6.3) and mean survival time of 3.6 years for chemotherapy (95 % CI 2.6 to 4.7). Although this was

statistically significant, it may be that primary surgery was done mainly for early stage disease and neoadjuvant chemotherapy was done for the advanced cases.

There was a statistically significant difference in time to recurrence between early and late stages. There were only three recurrences in the early stages, with mean survival time of 5.9 years and 25 recurrence in the advanced stages with mean survival time of 2.7 years (p value <0.001) .

The survival rate was 91.50% for optimally reduced with mean survival time of 5.7 (95%C.I 5.34 to 6.13) and survival rate of 70.6 % for suboptimal cytoreduction with mean survival time of 3.7 years (95%C.I 2.25 to 5.09). This was statistically significant (p value 0.003). The time to recurrence for the optimal and suboptimal group showed progression free survival rate of 70% and 41% with given mean survival time of 4.66 and 2.43 years (p value 0.002). Most studies have shown that optimal cytoreduction is the most important prognostic variable, at least the one variable that something can be done about. In recent years the definition of optimal cytoreduction has moved from less than 2 cm residual to 1 cm and currently to zero residual.

There are a number of Indian studies on germ cell tumors as well as sex cord stromal cell tumors. One study done over a period of 11 years recruited 23 patients with a median age of 19 years. The study wanted to find out if neoajuvant chemotherapy followed by interval debulking would help those with bulky tumor (7). Neadjuvant chemotherapy followed by fertility sparing surgery could be a reasonable option for malignant GCT not suitable for

optimal cytoreduction surgery (58). Another Indian series on 28 cases of Immature ovarian teratoma done in a group with median age of 19 years(59), most common presentation was pain abdomen. Neuroepithelium was seen in 26 cases of which 6 had grade1, 13 had grade 2, and 7 had grade 3. (59). There were 7 deaths during a median follow up of 33 months. Another study which tries to find out if there could be a role for aggressive cytoreduction surgery for non-dysgerminoma mature tumor, in these study with 33 patients with germ cell tumor ,12 had EST ,11Dysgerminoma,7 with Mixed GCT, and 3 with Immature Germ cell tumor, this study indicate that there could be a role for aggressive cytoreduction. In another study on 27 patients with pure dysgerminoma of the ovary done in Mumbai (60), 2 of 10 patients in stage I patients underwent unilateral salpingo-oophrectomy ,with no further adjuvant chemotherapy; the rest underwent total abdominal hysterectomy with bilateral salpino-opherectomy (TAH / BSO) followed by adjuvant chemotherapy; Patients in stage II and stage III had total abdominal hysterectomy followed by postoperative radiotherapy . One patient presented in stage 1V and three patients with recurrence after a full treatment in another center. The disease free as well as overall survival at 108 months for the 24 cases primarily treated at Mumbai was 81% and 88%, and for patients in stages I and II 100% (Kaplan-Meier estimation). The study stressed the need for controlled clinical trials to devise optimal therapy in early clinical stages and use of chemotherapy for advanced disease, for this highly curable disease.

A study was done to see outcomes of malignant ovarian germ cell tumors treated in Chiang Mai University Hospital over a nine year period.(15) This was a clinico-pathological and survival study. Of the 72 cases recruited, the mean age was 21.6 years and 11.8% were pre-

menarchal. The two most common symptoms were pelvic mass and pelvic pain. Two-thirds of the studied patients presented at an early stage. The common histology in descending order of frequency were 1. immature teratoma (34.2%) 2. endodermal sinus tumor (28.9%),3. dysgerminoma (25%),4. mixed type (10.5%) and 5.choriocarcinoma (1.3%). Treatment with fertility sparing operations and adjuvant chemotherapy with a BEP regimen showed a good outcome. An advanced stage was found to be a risk factor for recurrence.

Of the 9 mixed germ cell tumors seen in our series, 5 were stage III or IV,and four were stage I or II. Of the immature type, 3 were stage III and 2 were stage 1a; of the four yolk sac tumors, 1 was stage 1V and 3 were stage 1a to 1c, and of the dysgerminomas, 1 was stage Ia, another Ic and the third IIa. The survival rate for early stage was 100% and advanced stage was 74% with overall survival of 87%.

A study on Granulosa cell tumor done over a 10 year period showed(61) the good prognostic factor for this tumor was optimal cytoreduction(p 0.02). Presence of nuclear atypia($p<0.001$), increased mitosis(0.03) were the other factors that impacted survival significantly. Age, stage of the tumor, parity and size of the tumor had no significant effect on survival. Patients who had chemotherapy had median survival of 60 versus 48 than those who did not have, but it was not statistically significant (p value 0.08)

A Chinese study on 46 patients with granulosa cell tumor over a period of 10 years showed that FIGO stage (p value of 0.00030), presence of nuclear atypia (p value 0.036) and, increased mitosis (p value 0.0020 were three factors that impacted survival(62).

Regarding grade of the tumor, of the 93 patients in our study, 15(16.1%) had well differentiated type, 13(13.9%) were moderately differentiated and, 21(22.5%) poorly differentiated.

Perfomance status of a patient has prognostic value as with residual disease after surgery and volume of ascites. Of the 93, performance status was documented for 87 patients, 36 of them had ECOG of 0, 45 with ECOG 1 , 5 with ECOG of 2 and I with ECOG 3.

53 of the 93 had no gross residual tumor, 15 had less than 1 cm residual (optimal cytoreduction) , 19 had > 1 cm residual and three had open laparotomy with biopsy .

For secondary treatment of the disease 5 had surgery, 23 had chemotherapy, I had radiotherapy, 1 (androgen secreting tumor), and 31 patients did not have secondary treatment with us.

Surgical staging was done according to FIGO (International federation of Gynecology and Obstetrics)1988.47 of the 93 were staged as Early (from stage 1a to stage 2c) and 46 patients were staged as advanced stage from Stage 3a to stage 4) .

23 of our patients had fertility sparing surgery, it was found out that three of our patients had become pregnant and had given birth.

Early stage disease and non epithelial histology had the best prognosis in multivariate analysis.

Cox proportional hazard model are used to determine the endpoint effect of variables like histology,primary treatment ,surgery vrs chemotherapy and residual disease on survival,early stage disease and non epithelial histology had the best prognosis in multivariate analysis.

The important reasons for poor patient compliance and follow up to the primary treatment are financial constraints. Surgery and chemotherapy are beyond the means of almost a third of our population. Most patients do not have insurance. The other reason for poor follow up to cancer care is lack of knowledge. The patient and family are not aware of the importance of follow-up and the possibility of recurrence. Poor communication by health professionals and a lack of health infrastructure compound the problem. . In our country illiteracy and poverty play a role for the above limitations.

LIMITATIONS and STRENGTHS

Limitations : This study analysed available data of all the patients who underwent surgery for ovarian tumor in our hospital during a 5 year period from 2008 to 2012. The major limitation of our study is that 18 % of patients who are completely lost to follow-up after surgery. Information on the others was also gained in the main part by phone calls and letters. It was a big challenge to contact our patients as telephone numbers were often not provided. Also telephone and postal numbers provided to the hospital were incorrect or had not been updated. There could be a bias in the follow up in that there could have been more complications, recurrences and deaths in the 27 women who were completely lost to follow up. Since this was mainly a retrospective analysis, collection of information could have been incomplete with a differential bias

Another limitation was the small number of events. Only 10 deaths had been identified in the 76 patients that were followed up. This made risk factor analysis difficult. Statistical assumptions could have been violated in the multivariate analysis.

Strengths : This study is one of the first to look at ovarian cancers in young women. At the Christian Medical College Hospital, medical records, laboratory data and radiological reports are stored electronically hence access and retrieval to patient information is relatively easy. In the past few years more and more patients and their family members have mobile phones and can be contacted.

Another strength of this study was the good statistical analysis as the institution has a well established department of biostatistics. Survival analysis could be done stratified for the important variables such as stage of disease, primary treatment and histological type of cancer.

Suggestions for improved care : In order to improve our comprehensive cancer treatment services, capacity building of all the professionals responsible for patient care as well as documenting and storing medical records of the patients is essential. There has been a push for a Cancer Registry for the country. Standardizing our diagnostic methods and our treatments so that these can be audited for quality improvement is to be encouraged. All the professionals concerned should follow a minimum standard of reporting and documentation. Electronic entry of all information about the patient, contact address, email and phone numbers would make follow up and ascertainment of disease status easier.

The employment of social workers to contact defaulters and referral to professionals nearer the patient's home would ensure that compliance to treatment is enhanced.

CONCLUSIONS

(1) Even in women 40 years and less, 70 % of the ovarian tumors were epithelial in histological type. Serous ovarian cancer was the most common.

(2) Germ cell tumor constituted 20 % of the ovarian cancers. Mixed malignant germ cell tumor was the commonest type.

(3) The mean overall survival was 5.4 years. The overall survival was 87%.
For epithelial tumors it was 82 % and for non-epithelial tumors it was 96 %.
For early stage disease it was 100 % but for advanced stages it was 73 %.

(4) Disease recurrence was seen in 37 %. The mean overall progression free time was 4.3 years. For epithelial tumors it was 3.8 years and for non-epithelial tumors it was 5.3 years. For early stage disease it was 5.9 years and for advance stages it was 2.7 years.

(5) Early stage disease and non-epithelial histology had the best prognosis in multivariate analysis.

IMPLICATIONS

This study has reiterated that early diagnosis, aggressive surgical debulking and compliance to chemotherapy are the most important factors that determine outcome in young women with ovarian cancer. Treatment of such cancers should be done in specialized cancer centers or gynecological oncology units of tertiary level hospitals.

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ANNEXURES

ANNEXURE I ABBREVIATIONS

AFP	Alpha fetoprotein
BMI	Body Mass Index
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial ovarian cancer
FIGO	International Federation of Obstetrics and Gynecology
GCT	Germ cell tumor
H CG	Human Chorionic Gonadotropin
ICMR	Indian Council of Medical Research
LDH	Lactate Dehydrogenase
PFS	Progression free survival
SPSS	Statistical packages for social sciences
TNM	Tumor node and metastasis

ANNEXURE II

INFORMED CONSENT

Participant Information Sheet

Christian Medical College, Vellore.

Department of Obstetrics and Gynaecology

Study on Follow –up of women under 40 years with ovarian cancer

You are being requested to participate in a study to see how women under 40 years present with cancer ovary , what treatment was given and how did they respond to the treatment , we hope to include about 70 women in the study.

What is the need for the study. – Cancer of the ovary is one of the commonest cancer in women, therefore we are starting this study so as to gain further knowledge about this disease in young women.

Is there a harm to you in participating in this study

No harm will be done, as your privacy and confidentiality will be respected.

If you take part I what will you have to do

It is to permit us to review your medical records and few questions regarding your state of health will be asked of you.

Can you withdraw from this study after it starts your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to study in this study ,if you do so this will not affect your usual treatment in this hospital in any way.

Will you have to pay for this study No payment is required for this study ,any other treatment that you usually take will continue and the routine charges for the treatment will be paid by you.

Will your personal detail be kept confidential? The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of the results, however your medical notes may be reviewed by people associated with the study without your additional permission if you are included in this study.

If you have any further questions please ask Dr. Eileen Lalrinpuii (918056755392), Dr.Abraham Peedicayil: or email to og1@cmcvellore.ac.in

Format for Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title: Out Come of Women 40 Years and below with Cancer ovary

Study Number: _____

Subject's Initials:_____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

April 07, 2014

Dr. Eileen Lalrinpuii
PG Registrar
Department of Obstetrics &Gynaecology
Christian Medical College, Vellore 632 004

Sub: **Fluid Research grant project:**
Outcome of women 40 years or younger with ovarian cancer.
Dr. Eileen Lalrinpuii, PG Registrar, Dr. Abraham Peedicayil,
Dr. Ajit Sebastian, Assistant Professor, Dr. Vinotha Thomas, Assistant Professor, Dr. Anitha Thomas, Associate Professor, Dr. Rachel Chandy, Obstetrics & Gynaecology, Dr. L. Jeyaseelan, Biostatistics, CMC, Vellore

Ref: IRB Min No: 8725 [OBSERVE] dated 06.03.2014

Dear Dr. Eileen Lalrinpuii,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Abraham Peedicayil, Obstetrics & Gynaecology, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Ref: IRB Min No: 8725 [OBSERVE] dated 06.03.2014

Dear Dr. Eileen Lalrinpuii,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Outcome of women 40 years or younger with ovarian cancer." on February 19, 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Eileen Lalrinpuii, Abraham Peedicayil, Ajit Sebastian, Vinotha Thomas, L. Jeyaseelan, Anitha Thomas, Rachel Chandy, Abraham Peedicayil
3. Informed Consent form (English, Hindi, Tamil & Bengali)
4. Consent form (English, Hindi, Tamil & Bengali)
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 19, 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. J. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Ranjith K Moorthy	MBBS M Ch	Professor, Neurological Sciences, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMCH.	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, Ph D, MAMS	Professor, Cardiology, CMCH.	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC	Internal, Clinician
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMCH	Internal, Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMCH	Internal, Legal Expert

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Shirley David	M.Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMCH	Internal, Nurse
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMCH.	Internal, Scientist & Pharmacologist
Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMCH.	Internal, Nurse
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMCH.	Internal, Clinician
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in

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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 20,000/- INR (Rupees Fifty Thousand only) will be granted for 1 year.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD., MNAMS., DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

NOT TO BE MINISTERED UNTO BUT TO MINISTER
CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

Cc: Dr. Abraham Peedicayil, Obstetrics & Gynaecology, CMC, Vellore

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2	471233A		34				1			1	2					1	1	2	145				2		2	2	2	1	2	2	0	0	2	0	1	2	2	1		8	9	1	1	2		2				
3	219261D	9437249634	22	156	75	1	2			0	3	2	2	2	2	3	2			1250	422	7.46			1	3	2	1	2	2	0	0	2	0	1	2	2	11	3	9	5	2	6	2		2	2		2	04/08/2014
4	240933D	8.80182E+12	22		52	1	2	2		1	4	2	2	2	2	1		2	8.2					4.4	1	2	1	1	2	2	2	2	2	2	1	2	2	2	1	1	2		6	1		2	2		2	07/08/2014
5	942295C		36			0	2				3	2	2	2	2	1			26.5						1		2	1	2						1	2	2												
6	192739D	9734772915	30	157	53	1	2	1	96		3	2	2	2	2	1	2	2	13.7					4.9	2	1	1	1	2						1	2	2	2		1	2	2	1	2		2	2		2	04/08/2014
7	040181D		36	155	60	2	2	1	9	1	4	2	2	2	2	2			5.53				1		1	1	2	1	2	2	0	0	2	0	1	2	2	9	5	1	6	2	6	2	4	2	2		2	27/12/2013
8	363954D	9895396873	27	149	45	1	2				2	2	2	2	2	3				7	1740	72.1		2.9	1	1	1	2	2	2	10	0	2	0	1	2	2	11	1	7	9	2	6	1	1		2		2	08/08/2014
9	276135D	9333438595	40	144	40	2	1			1	2	2	2	2	2	1	1	2	4620					4.8	2	1	2	1	2	2	0	0	2	0	1	2	2	1	2	9	2	1							
10	318102D	9835117977	33	153	64	1	2			2	2	2	2	2	2	1	1	2	661				2	2.8	2	3	2	1	2	2	0	0	2	0	1	1	2	3	2	7	2	2	2	2	1	2	1	07/04/2011	1	20/03/2012
11	406832D	9443956693	21	144	65	0	2	2		2	3	2	2	2	2	3	2		15.8	1.22	2730	286	2		1	1	1	2	2	2	1	0	2	0	1	2	2	6	5	3	5	2	6	2	4	1	2		2	23/08/2014
12	424459D		33		58	2	2				3	2	2	2	2	1			10.6				1		1	1	2	1	2	2	0	0	2	0	1	1	2	2	1	1		2	6	2	4	2				
13	472173d	9885257468	26			2	1			2	3	2	2	2	2	3	2		20.4	1.34	6804	122	2		1	1	1	2	2	2	1	0	2	0	1	2	2	11	5	3	5	2	6	2	1	2	2		2	06/08/2014
14	476103d	9732511620	34	144	33	0	2	2	2	1	2	2	2	2	2	1	1	2			827	30	1	2.6	1	1	1	2	2	2	7	4	2	0	1	2	2	2	5	10	2				4					
15	512728d	9732981850	18	157	57	0	2	2		0	3	2	2	2	2	1		2					1		1	1	1	2	2	2	0	0	2	0	2	2	2	11	5	10	9	2	2	1		2	1	20/07/2009	1	10/01/2010
16	519833d	9894293869	32	155	46.6	3	1	2		0	3	2	2	2	2	1	2	2							1	1	2	1	2	2	0	0	2	0	1	2	2	2		9	2	2	6	2	4	2	1	04/03/2011	1	27/03/2011
17	567463d	9847513212	37	157	40	1	2			1	3	2	2	2	2	1		1	84.4				1	3.5	2	1	2	1	2	1	0	0	2	0	1	2	2	11	3	9	2	1	6	3		2	2		2	20/03/2014
18	579099d	9491641779	36	143	37	3	1			2	4	2	2	2	2	5	1						1		1	1	2	1	1	2	0	0	2	0	1	2	2	11	5	5								
19	594798d	4182460871	30	159	56.6					2	4	2	2	2	2	1		2					2		1	1	2	1	2	2	0	0	2	0	1	2	2	1	4	1		2	6	1		2	2		2	28/08/2014
20	638777d		23	142	45	0	2	2		0	3	2	2	2	2	1			29	24500		1	2		1	3	3	2	2	2	0	0	2	0	1	1	2	11	5	9	5	2	6	2	1		2	01/03/2012		
21	071177d	9943060895	37	164	43	2	1			1	3	2	2	2	2	1								3.4	2	2	2	1	2	2	0	0	2	0	1	2	2	1	3	10	2		2	2			1	01/11/2011		
22	779072d	9832089878	36	154	38.2	0	2	2		2	3	2	2	2	2				54.68				2	4	1	1	2	1	2	2	0	0	2	0	1	2	2	11	2	3									
23	795351d		35			2	2			0	4	2	2	2	2	2			5.14				1	3.5	1	1	2	1	2	2	0	0	2	0	1	2	2	9	5	3					4					

24	795758d		28	145	35	1	2			1	3	2	2	2	1	1		2	136					4.5	1	1	1	1	2	2	0	0	2	0	1	2	2	1	5	3	2	2		2		2	2	14/09/2012		
25	822046d	9088474258	28	146	40.4	0	2	2		0	2	2	2	2	2	1	2		100	0.98	379	0.152	1	4.2	1	1	2	1	2	2	0	0	2	0	1	2	2	1	5	2	2	2	6	3	3	2	2		2	03/09/2014
26	823989d	7872633824	40	156	38.8	2	2	1		1	3	2	2	2	2	1	1	2	2360				1	3.7	1	1	2	1	2	2	0	0	2	0	1	2	2	11	1	1	2	2	6	2	1	2	2		2	08/01/2014
27	859958d	8682960073	21	147	40.9	0	2			1	2	2	2	2	2				61.9	642	455	0.373		4.1	1	1	1	2	2	2	3	0	2	0	1	2	2	11	1	1		2	6	2	4	1	2		2	17/08/2014
28	914506d	1710833642	39	177	65	2	2	2		2	3	2	2	2	2		1						1	4	1	4	3	2	2	2	0	0	2	0	2	2	2	11	5	10	9	2	6	1		2	1	01/03/2011	1	24/05/2011
29	359769c		31	154	60	0	2	2		0	3	2	2	2	2		2		26.6				2		1	1	1	1	2	2	0	0	2	0	1	1	2	1	2	3	2	2	6	2	1	2	2		2	18/06/2014
30	973216d	9933709472	40	158	52.6	3	2			0	4	2	2	2	2	1			10.5					3	1	1	2	1	2	2	0	0	2	0	1	1	2	2	1	1		2	6	2	4	2	2	22/07/2013		
31	923183d	94349860721	34	159	74	1	2	1	192	1	3	2	2	2	2		2		7.09				2		1	1	1	1	2	2	0	0	2	0	1	1	2	2	1	3	2	2	6	2	1	2	2		2	04/08/2014
32	941050d		32	149	40.36	0	2	2		1	3	2	2	2	2		1	1	248	850	892	0.8	2	3	1	3	2	1	2	2	0	0	2		1	2	2	11	3	8										
33	892253d	9171544637	28	156	48.1	0	2	2		0	4	2	2	2	2	1		2	15				1	4.8	2	1	1	1	2	2	0	0	2	0	1	2	2	11	3	9	2	1	2	2	4	2	1	24/05/2012		
34	595385d	9446184930	33	165	72	2	2			2	4	2	2	2	2	4			33.2					4.3	1	3	2	1	2	2	0	0	2	0	2	2	2	11	5	9	9	2	1	1	1	2	1	04/09/2013	2	08/09/2014
35	963354d	909233799	23	145	39.2	0	2	2		1	2	2	2	2	2	1		1	485	84.6	511	0.1	2	4	1	1	1	2	2	2	0	0	2	0	1	2	2	11	3	9	2		1	2		2	1	19/07/2013	2	17/08/2014
36	951621d	9430104504	31	158	62.8	2	2			0	4	2	2	2	2				7.3	0.64		1	1	5	1	1	1	2	2	2	0	0	2	0	2	2	2	9	2	1		2		1		2	2		2	24/08/2014
37	755895b		36	160	65.5	1	2			1	3	2	2	2	2	3		2	122	1.33	380		2		2	1	1	1	2	2	0	0	2	0	1	2	2	11	3	1	5	1	6	2		2	2	24/02/2014		
38	970454d	9895039750	40	150	70.5	1	2	2		1	3	2	2	2	2	1		2					1		1	1	2	1	2	1	2	0	2	0	1	2	2	2	1	9	2	1	2	3	4	2	1	09/08/2011	2	28/08/2014
39	989904d		32	154	82.58	2	2			1	2	2	2	2	2	1	1	2	428	1.64			1	2.9	1	1	2	1	2	2	0	0	2	0	1	1	2	2	1	10			1	2		2				
40	012317f	9681194893	29	153	49.6	0	2			0	3	2	2	2	2	1			27.7				2		1	1	1	2	2	2	0	0	2	0	1	2	2	1	1	1		2	6	2	4	2	2	13/05/2013		
41	024261d		34	163	34	2	2	2		0	4	2	2	1	2		2		52.6				1		1	1	2	1	2						1	2		1	1	3										
42	024823f	9781856399	31	147	54.8	0	2			0	1	2	2	2	2	1	1		150.8				2		1	1	1	2	2	2	1	0	1	0	1	1	2	3	1	3	2	2	6	2	4	2	2		2	04/08/2014
43	020157f	9973848121	18	154	41.4	0	2	2		1	3	2	2	2	2	1		1	491	0.63	409		2		1	1	2	1	2	2	0	0	2	0	1	2	2	1	1	7	2	2	6	2	1	2	2		2	23/08/2014
44	017813f		40	150	58	2	1			1	3	2	2	2	2		2	2	896					4.4	1	3	2	1	2	1	0	0	2	0	1	2	2	1	5	8	2	2	2	2	4	2	1	27/08/2012		
45	972680d	8972142036	37	161	52.2	2	1			1	2	2	2	2	2	1	1		19100				1	3.6	2	1	2	1	2	2	0	0	2	0	1	2	2	11	3	10	2	1	3	2	1	2	1	13/06/2012	1	12/10/2013
46	056559f		32	168	71.6	0	2	2		1	3	2	2	2	2				2740				2		1	1	2	1	2	2	0	0	2	0	1	1	2	1	2	5	9	2	6	2	1	2	2		2	18/08/2014
47	057844f	9832011179	26	150	36.06	1	2			0	3	2	2	2	2	1		2	70.1	1.51		20.1	2		1	1	2	1	2	2	9	0	2	0	1	2	2	2		9	2	2	2	2		2	1	12/02/2012		

48	076668f	9035089835	19	155	46.2	0	2	2		1	3	2	2	2	2					0.95	672	0.1			1	1	1	2	2			0	2		1	2	2	11									2		2	24/08/2014
49	075600f	9973661455	34	146	49.7	1	2			0	3	2	2	2	1		2		77.4				1	4.7	1	2	2	1	2	2	0	0	2	0	1	2	2	1	5	9	9	2	6	2		2	2		2	22/09/2014
50	091817f	9973788278	37	167	81.8	2	2	2		0	1	2	2	2	2	1		1							1	1	1	2	2						2	2	2	5	5	1										
51	093556f	9424253550	26	161	52.8	0	2	2		0	4	2	2	2	2	3		2	590	1600		0.509	2		1	3	1	2	2	2	0	0	2	0	1	2	2	11	5	9	5	2	6	1	4		2		2	24/07/2014
52	086490f		32	151	57	1	2			0	4	2	2	2	2	1	2	2	97.5	7.84	501	41.8	2	4.8	1	2	1	1	2	1	0	0	2	0	1	1	2	1	3	7	2		2	2		2	1	20/12/2013	2	11/08/2014
53	099941f	9546787502	27	150	52.7	2				0	3	2	2	2	2	1	2	1	118	1.3	323	0.1	2		1	1	1	1	2		4	0	2	0	1	2	2	1	2	2	2	2	6	2			2		2	31/01/2014
54	131776f	9831715039	30	153	47.6	0	2	2		1	2	2	2	2	2	1	2		35.6						1	1	1	2	2	2	0	0	2	0	2	2	2	2	4	1		2	6	1			2		2	24/08/2014
55	123266f	9489319740	30	144	47.9	1				0	3	2	2	2	2				48.1						1	2	1	1	2	2	0	0	2	0	1	1	2	3	1	5	2	1	2	2		2	2		2	17/08/2014
56	103103f	8015133809	22	164	45.2	0	2			0	3					1		2	8902						1	1	3	2	2	2	1	0	2	0	1	1	2	1	4	1	9	2	6	1		2	2		2	22/05/2014
57	065091f	9835574614	38	155	62.4	2	1	2		0	2	2	2	2	2	1	1	1	17700		473		1	3.2	2	2	2	1	2	2	0	0	2	0	1	1	2	11	3	10	2	1	2	2		2	1	06/02/2014	2	24/08/2014
58	365568f	8900691122	31	166	62.7	6	2	2		0	2	2	2	2	2	1	1	1	23.78					2.6	1	3	2	1	2	2	0	0	2	0	1	2	2	1	5	9	2	2	6	2		2	2	08/04/2013		
59	569636b	8900691122	40	150	43.3	0	2			0	3	2	2	2	2	1	2	2	72.4		248			4.5	1	1	1	1	2						1	2	2	1	5	4	2	2	6	2	4	2	2	24/03/2014	2	
60	125849f	8900691122	34	149	39.4	3	1			0	2	2	2	2	2	1		2	4.85				1	3.4	2	3	2	1	2	2	0	0	2	0	1	2		11	5	10	2	1	2	2		2	1	04/10/2014		
61	159982d	35122258940	24			0	2	2		1	3								59.8						1	1	1	2	2	2	0	0	2		1	2	2	1	4	3		2	6	2		2	2		2	14/08/2014
62	219262f	9.19732E+11	33	163	42.3	2		1		1		2	2	2	2	3	1		203	672	756	0.317	1		1	3	2	1	2	2	0	0	2	0	1	2	2	11	3	8	5	2		2		2	2		2	02/09/2014
63	827838d	9732151583	31	153	50	1	2			0	2	2	2	2	2	1	2	2	25.23	672	406	0.317	1		1	1	1	2	2	2	0	0	2	0	2	2	2	2	4	1	5	2	6	1		2	2		2	20/02/2014
64	182372f	9933524081	32	155	58.2	0	2	2		1	2	2	2	2	2	1		2	3570					3.7	1	2	2	1	2	2	0	0	2	0	1	2	2	11	3	9	2	2	2	2		2	1	04/12/2013	2	14/08/2014
65	268523f	9931589613	17	169	52.5	0	2	2		0	4	2	2	2	2		2		0.48	543	0.1	2.27	1		1	1	1	2	2	2	0	0	2	0	1	1	2	2	4	1		2	6	2		2	2		2	24/08/2014
66	983009c	9894775721	27	158	84	1	2	2		1	4	2	2	2	2	1							2		1	1	2	2	2	2	11	1	1	0	1	1	2	1	5	5	2	2	6	2		2	2		2	07/07/2014
67	312101d		35	155	47.4	4	1			0	3	2	2	2	2	1	2	2						4.5	1	1	1	1	2	2	0	0	2	0	1	2	2	3	1	3	2	2	2	2		2	2	30/06/2010		
68	209732f	9735035574	32	158	60	1	2	2		0	3	2	2	2	2	1		2	69.5	0.5		0.1	1	4.5	2	3	2	1	2						1	1	2	1		10	2	1		2		2	2		2	18/07/2014
69	850664d	9608196126	21	157	44.4	0	2	2		1	3	2	2	2	2			2	35.7				2		1	1	2	1	2	2	2	0	1	1	1	2	2	1	1	2	2	2	1	2	4	2	1	18/05/2011	2	29/01/2013
70	207333f	9905165269	28	157	60.7	1	2	2		0	2	2	2	2	2	3	1	2	329	496274	855	1.7	2		2	3	2	1		2	11	0	2	0	1	1	2	7		10	6	1	2	2		2	1	25/07/2013	2	17/08/2014
71	123371d	9865447642	30			4	2			1	2	2	2	2	2	1	1	1	6910					2	2	3	2	1	2						1	2		11	5	10	2	1	1	1						

72	192664d	9474608819	39	162	84	1	2	2		1	4	2	2	2	2	1								4.3	1	2	2	2	2	2	0	0	2	0	1	2	2	1	5	9	2	2	2	2		2	1	16/06/2009	2	30/06/2010
73	143860d	947435747	27	150	38	0	2			1	2	2	2	2	2			2	1.4			1	1	2.6	2	3	1	1	2	2	0	0	2	0	1	2	2	1	3	5	2	1	2	2	4	2	1			
74	168668d	9436142985	39			1	1			1	3	2	2	2	2	1		2	500					3.8	2	3	2	1	2	2	0	0	2	0	1	2	2	11	2	9	2	1	2	2	2	2	1	19/09/2008	1	27/05/2009
75	849636c		38	155	36	1	2			1	4					1		2	221					2.3	1	1		1	2	2	0	0	2	0	1	2	2	1	5	9	9	1	2	2	4	2	1	13/07/2009	2	27/04/2010
76	225424d	9933607561	36	147	48	2	1	2		1	4	2	2	2	2	1			70.9					3.2	1	1	2	1	2	2	0	0	2	0	1	2	2	2	4	1		2	6	2	4	2	2			
77	213770d	9436168614	38			1	2			1	3	2	2	2	2	1		1	33.7					2	2	4	3	2	2	2	2	2	2	2	2	2	2	11		9	9	2	6	1		2	1	30/05/2008	1	11/07/2008
2	352807c	9791648239	21	150	40		2	2		1	2	2	2	2	2	1	1	1	258	1.27	609	1		4.9	1	1	1	2	2	2	0	0	2	0	1	2	2	1	4	3	2	2	6	1	1	2	2	07/06/2013		
79	338257d	9051208170	21	157	59		2	2		2	2	2	2	2	2	2	2		87.4	1.22	509	1		4.6	1	1	1	2	2	2	0	0	2	0	1	2	2	11	5			2	1	2						
80	136043d	4171245136	28			2	1			0	2	2	2	2	2			2	86					4.4	1	2	1	1	2						1	1	2	2	4	8	2		2	1	4	2				
81	354114d	933134010	28	154	66.3	2	1	1	12	0	4	2	2	2	2	3		2	22.9	1.6	2380	2380			1	1	1				3	0			1	2	2	6	5	1	9		6	2	4	2	2	20/03/2013		
82	385829d	9852085847	35	155	73	3	1	2		0	4	2	2	2	2	1		1	20.9					4.4	1	1	1	2	2						1	2	2	1	4	3	2	2	6	2			2		2	07/09/2014
83	191912c		30	157	63.5	2	1			1	2	2	2	2	2		1		6.37					4.7	1	1	2	1	2	2	0	0	2	0	1	2	2	11	5	3	9	2	2	2	4	2	1	26/07/2014		
84	068053D	8572283465	18	158	35.5	0		1	2	1	3	2	2	2	2	3	1	1		2640	1081	54.8		4.2	1	1	2	2	2	2	0	0	2	0	2	2	2	6	3	7	5	2		1		2	2	09/07/2012		
85	470090D	9474523470	32	153	70	2	1			1	3	2	2	2	2	3		2	102	3770	853	1		4	1	1	1	1	2		1	0	2		1	2	2	7	5	3	9	2	2	2			1	01/09/2014	2	14/03/2014
86	435216D	9954984186	39	147	41.7	3	2			1	3	2	2	2	2	1		1	68.3					4.6	2	1	2	1	2	2	0	0	2	0	1	2	2	11	3	9	2	1	2	2		2	1	01/12/2010	1	23/12/2011
87	495937d	943116738	32				2	2		0	4	2	2	2	2		1	2	195				2		1	4	3	2	2	2	0	0	2	2	2	2	2	11	3	10	9	2	6	1	4	2	1	23/07/2009	1	09/08/2009
88	486913d	9685200303	22	160	30.8		2	2		0	3	2	2	2	2	5	1	2	86.8	2.22	471	1.96	1	2.6	2	4	3	2	2						2	2	2	11		10	9	2	2	1	4	2	1	19/11/2009	1	19/04/2010
89	520836d		35	156	49.3	0	2	2		1	3	2	2	2	2	1	2	2	32.4				2	4.3	1	1	1	1	2	2	0	0	2	0	1	2	2	1	2	2		2		2		2				
90	551046d	19436118019	39	151	55.8	2	2	2		0	4	2	2	2	2	1	2	2						4.5	1	1	2	1	2	2	0	0	2	0	1	2	2	3	1	1		2		2	1	2	2		2	20/08/2014
91	424771d	9748906049	37	151	52.8	1	2			1	3	2	2	2	2	1		2	73.2					4.1	2	3			2	2	0	0	2	0	1	2	2	11	3	10	2	2	2	1		2				
92	698040d	9234431261	23	154	56		2	2		1	3	2	2	2	2				140.1	5430	1300	155.7		3.3	1	2	1	2	2	2	0	0	2	0	1	2	2	11		6	5	2	6	2	1	2	2		2	09/09/2014
93	705794b	9444236576	33	150	96.4	2	1			1	3	2	2	2	2	1		2	11.2					4.6	1	1	1	1	2	2	0	0	2	0	1	2	2	2	2	3	2	2	6	2	4	2	2		2	08/09/2014
94	814629c	9443164847	28			1	2			0	4	2	2	2	2	1		2	9.84	1.66	520	1		1	1	1	2	1	2						1		2	2		1		2	6	2		2				
95	648872d	9346815702	25	150	39.2	0	2	2		0	4	2	2	2	2		2						1	4.9	1	1	3	2	2	2	0	0	2	0	2	2	2	11	5	1	9	2	5	1		2	2		2	23/08/2014

96	754678d		36			1	2	2		0	3					3		2	2	138	420	6142			1	1	3	2							1	2	2	7		1	5			1			2	12/02/2011		
97	574461d	9933757382	28	149	51	1	2	1	48	1	1	2	2	2	2		2	1	149	5.5	676	1			1	2	2	1	2						1	1	2	2	5	10	2	2	2	2		2	1	01/02/2010		
98	829356d	9774156903	17	160	53		2	2		0	3	2	2	2	2	1		2	2.36	1.48		1		5	1	1	1	2							1			2		6	2	2		2			2	17/06/2011		
99	136529f	9494032611	34	155	64	1	2	2		0	3	2	2	2	2				21.2				1	4.1	1	1	2	1	2	2	0	0	2	0	1	2	2	11	5	3	2	2	6	2		2	2		2	17/08/2014
100	498835c		26			0	2	2		1	4					2		2					1		1		2	1	2	1	0	0	2	0	2	2	2	8	3	4	6	2	1			2	1	03/08/2004	2	15/03/2008
101	228700d	9790175645	39	155	62	2	1			1	3	2	2	2	2	1	2							4.4	1	1	2	1	2	2	0	0	2	0	1	2	2	2	5	3	2			2	4	2	2		2	06/08/2014
102	248993d	9790175645	35	146	66	0	2			1	2	2	2	2	1	1	2	2	1690					3.6	1	1	2	1	2	2	0	0	2	0	1	2	2	2	4	3	2	2	6	2	4	2	2		2	17/08/2014
103	203506d	9732330980	38		63	1	2			1	2	2	2	2	1	1	1		5000					3.6	2	1	2	1	2	2	0	0	2	0	2	2	2	11		9	2	1	2	1	4	2	1	01/12/2008	1	10/04/2010
104	260168d		13		30	0	2	2		3	3	2	2	2	2	3			197	30000	2040	4.88	2	3.3	1	2	1	2	2	2	0	0	2	0	2	2	2	7	5	3	5	2	6	1	1	2	2		2	08/05/2014
105	286097d	9.19995E+11	35	157	57.8	2	2	2		1	4	2	2	2	2				365						1	1	2	1	2						2	2	2	3	1	4	2	2		1		2	2		2	23/07/2014
106	311692d		26			2	2			1	2	2	2	2	2	1	1		413	1.03	534	1	1	3.6	1	3	2	1	2	2	0	0	2	0	1	2	2	11	3	9	9	2	6	2	4	2	1	24/10/2008		
107	415338d	9788696882	16	157	45		2	2		1	2	2	2	2	2				99.2	14700	2733	7.04		3.6	1	3	3	2	2	2	0	0	2	0	1	2	2	7	5	9	5	2	6	1		1	2	16/08/2010	2	
108	201324d		29	147	34	2	1			1	3	2	2	2	2			2	3220	0.95	646	1	2	3.4	2	1	2	1	2	2	0	0	2	0	1	1	2	7	5	10	9	1	3	2		2	1	14/10/2009	2	30/06/2010
109	979084c	9.19044E+11	37	155	62	3	1				2								16.7						1	1	2	1	2						2	1	2	2												
110	451494d	9647597841	19				2	2		1	2	2	2	2	2				67	654	3586	132		4.4	1	4	3	2	2	2	0	0	2	0	2	2	2	6		3										
111	926875c		35	160	64	3	1			1	2	2	2	2	2	1	1							3.9	1	2	2	1	2						1	2	2	1	4	3										
112	452338d	9434867897	40	148	59	1	2			1		2	2	2	2	1	1	2	916				1	4.1	2	2	2	1	2	2	0	0	2	0	1	2	2	11	3	10	2	1	6	2	4	2	2		2	25/07/2014
113	494308d	94747520	35	156	42.3	2		1		1	2	2	2	2	2	1	1	2	1348				1	2.2	1	1	2	1	2	2	0	0	2	0	1	2	2	11	3	9	2	2	2	2		2	1	25/06/2013	2	18/07/2014
114	390247d	9447838851	34	147	70	1	2			1	2					1	1		2920						1	1	2	1	2	2	0	0	2	0	1	2	2	1	3	8	2	2	2	2		2	1	01/06/2012	1	03/06/2012
115	755137d	944650885	18	164	50.4		2	2		0	3	2	2	2	2	3	2		35.2	1.19	1031	97.02	2	4.9	1	2	1	2	2	2	0	0	2	0	1	2	2	6		4	5	2	6	1			2		2	08/08/2014